ARSENIC IN COMMUNITY DRINKING WATER SYSTEMS AND SMALL FOR GESTATIONAL AGE BIRTH, PREGNANCY-RELATED HYPERTENSION, AND STILLBIRTH IN UTAH, 1989-2006

by

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ABSTRACT

The purpose of this dissertation research was to investigate whether there is an association between exposure to low to moderate levels of arsenic in drinking water in community water systems (CWSs) and small for gestational age birth (SGA), pregnancy-related hypertension, and/or stillbirth. The study included over 633,000 live births and stillbirths to Utah residents during 1989 to 2006 where the maternal addresses recorded on birth and fetal death certificates were within the boundaries of a CWS. Over 97% of the maternal addresses in each county were geocoded and then spatially linked to georeferenced data layers of 476 CWS service areas statewide and to elevation data. Water quality data collected for regulatory purposes were used to estimate annual average arsenic levels for each CWS; these values were assigned to the births and stillbirths based on the first trimester of the year of pregnancy and the CWS providing water to the maternal residence. Arsenic levels were less than 2.5 micrograms per liter (µg/L) for the majority of residences (73.8%); arsenic levels were greater than 10 µg/L at only 3.7% of the residences. There was a small but statistically significant association between arsenic concentration and SGA. Using <2.5 µg/L as the reference, the adjusted odds ratio (aOR) for SGA was 1.04, (95% confidence interval (CI) 1.00, 1.07) when arsenic levels were 5.1 to 9.9 µg/L (p-value 0.03), and aOR 1.07 (CI 1.03, 1.12) when levels were 10 µg/L or greater (p-value 0.002). At arsenic levels from 2.5 to 5 µg/L, there was a small, but not statistically significant (p-value 0.40), increase in SGA (aOR 1.01, CI 0.98, 1.04). Arsenic was not found to be associated with pregnancy-related hypertension, nor was there an association between low to moderate levels of arsenic in drinking water and stillbirth. An additional finding was that, compared with births at elevations less than 3,000 feet(ft), the frequency of SGA increased with every 1,000 ft increase in elevation to an aOR of 1.91 (CI 1.65, 2.22) for women residing above 6,000 ft.

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CHAPTER 1

INTRODUCTION

At high levels of chronic exposure, arsenic has been associated with a number of adverse reproductive outcomes, including preterm birth, lower birth weight, infant mortality, spontaneous abortion, and stillbirth (1-19). These associations, however, have not been demonstrated conclusively (20-21) due to study methodology, small sample sizes, and confounding by other occupational exposures.

Arsenic is a naturally occurring metal that enters drinking water sources through erosion and dissolution of rocks and minerals (22). Humans are exposed to arsenic through intake of food, water, and air (23). Exposure to arsenic in air is primarily through anthropogenic sources such as metal smelting, roasting of gold ores, coal or oil combustion, municipal waste incineration, and agricultural processes (23, 24). Natural sources of airborne arsenic exposure include dust from naturally occurring arsenic in soil, sea salt spray, volcanoes, fumaroles, and forest fires (23). Food is usually the major source of arsenic exposure; however, most adverse effects are attributed to exposure to arsenic in drinking water. The main reason is that in most foods arsenic is in the organic form of arsenic, while arsenic in drinking water is the more toxic inorganic form of arsenic, and is at relatively higher concentrations (25). Arsenic intake for a typical adult in the United States (US) is approximately 5 μg/day; however, intake in areas with high levels of arsenic in drinking water can be much higher (10-100 μg/day) (23). Preparing foods in arsenic-containing water can increase the arsenic content by 10-50% for most foods, and by 200-250% for foods that absorb cooking water such as beans and grains (26).

Groundwater arsenic levels vary across the US, with higher levels in many areas of the western states. In Utah, weathering of volcanic rocks and erosion of slag and soil from past mining activities are the major sources of arsenic in groundwater (27, 28). Arsenic levels in drinking water vary greatly throughout Utah, ranging from below the limit of detection to over 400 micrograms per liter (µg/l) in some private wells (27, 29).

Arsenic levels in public water systems have been regulated in the US since 1942, when the US Public Health Service set the standard at 50 micrograms per liter (µg/L). The US Environmental Protection Agency (EPA) adopted this standard in 1974 and set the initial Maximum Contaminant Level (MCL) at 50 µg/L (30). In 1993, the World Health Organization adopted an arsenic standard of 10 µg/L for drinking water (25). After decades of debate, the EPA lowered the MCL to 10 µg/L, effective January 2006 (31). Due to the expense of modifying infrastructure to reduce arsenic levels, the regulations permitted CWSs to apply for multi-year exemptions, allowing them more time to develop new water sources and modify water treatment equipment to reduce arsenic levels. Over 30 CWS in Utah were granted these exemptions (30). National drinking water standards do not apply to private wells, and no water monitoring or treatment is required for arsenic (32). The Utah Department of Natural Resources (UDNR) estimates that only 1.5% of residential water in Utah is supplied by private domestic wells (33). If risks for adverse reproductive outcomes are found to be elevated in those exposed to moderately elevated levels of arsenic (or other regulated contaminants) in drinking water, advisories may be indicated for alternative water sources for pregnant women whose drinking water sources are in water districts that do not yet meet EPA standards, as well as for testing of arsenic levels in private wells, particularly in residences of women of childbearing age.

Arsenic was one of the first chemicals recognized as a human carcinogen. In 1879, high rates of lung cancer in miners in Saxony was attributed in part to arsenic (34). A few years later, skin cancers were reported in patients treated with medicine containing arsenic. Chronic exposure to arsenic has also been associated with increased incidence of cancers of the bladder, skin, lung, kidney, and liver, cardiovascular disease, Blackfoot disease, and type 2

diabetes (4, 23, 31, 34-38). The largest known population impacted by arsenic contamination of groundwater is in Bangladesh, where the UNICEF programs in the 1970s developed wells and encouraged the use of groundwater instead of surface water for drinking (10, 39). While deaths from waterborne pathogens were significantly reduced through these efforts (40),arsenic-related health risks increased for the 35-77 million people now consuming water with very high levels of arsenic and other metals (39, 40).

Most studies of the effects of arsenic exposure have been conducted in countries such as Bangladesh, Chile, Taiwan, and India where there were very high levels of arsenic (>300 µg/L) in drinking water. Others studies were based on occupational exposures via air. There have been only a few studies of the health effects from chronic exposure to moderate levels of arsenic in drinking water (i.e., less than 50 µg/L), particularly in US populations. A cohort mortality study in Millard County, Utah, where arsenic levels ranged from 14-166 µg/L, found elevated levels of hypertensive heart disease and kidney disease (27). A study in Michigan, where the mean arsenic level in drinking water was 11 µg/L, provided additional evidence that serious health effects may result from exposure to lower levels of arsenic (41). These health effects included elevated mortality rates for circulatory system disease, cerebrovascular disease, diabetes mellitus, and kidney disease.

Arsenic readily crosses the placental barrier (23, 42), and several studies have found an increased incidence of reproductive and fetal developmental effects (genotoxic, mutagenic, and teratogenic) in a number of animal species (23, 31, 35, 43, 44). Epidemiologic studies have been inconclusive, and there are considerable knowledge gaps about the critical windows of exposure in humans (45). Additional studies with larger sample sizes have been recommended by the Agency for Toxic Substances and Diseases Registry to determine whether low to moderate levels of arsenic exposure contribute to adverse reproductive outcomes (23).

There are no well-defined biological mechanisms to explain the adverse effects of arsenic exposure on reproductive outcomes; however, several modes of effect have been suggested (46). Vascular endothelial cells are suspected to be primary targets of arsenic toxicity (4); studies have shown a dose-response relationship between arsenic in drinking water

and peripheral vascular disease, cerebrovascular disease, and carotid atherosclerosis (47-49). Since arsenic has been associated with these vascular effects, it is possible that arsenic may lead to some type of placental abnormality or decreased blood flow affecting fetal growth (15). Other theories include oxidative stress, interference with hormones, especially glucocorticoids and estrogen, or that increased methylation of arsenic during pregnancy may affect the fetus (42).

Three health outcomes were selected for this study: small for gestational age, pregnancy-related hypertension, and stillbirth. These were chosen because: a) they demonstrated strong associations with arsenic exposure in previous studies, b) they can be identified through use of vital records, and/or c) the relationship between the outcome and arsenic exposure has not been well established or study findings have been mixed.

Health Outcomes

Small for Gestational Age (SGA)

SGA is defined as an infant whose weight is less than the 10th percentile for gestational age. SGA is used a proxy for intrauterine growth restriction (IUGR) and its diagnosis requires knowledge of both birth weight and gestational age (50). Severely growth-restricted fetuses are at increased risk for stillbirth and neonatal death (50, 51). SGA has been associated with placental insufficiency (52), which is an hypothesized mechanism by which arsenic might adversely impact fetal growth.

Pregnancy-Related Hypertension (PRH)

PRH includes a group of life-threatening multisystem disorders, including eclampsia and preeclampsia, that generally occur after 20 weeks of pregnancy and include hypertension and proteinuria (53, 54). PRH is associated with preterm birth, perinatal morbidity and mortality, abruptio placenta, and IUGR (54, 55). There are very few studies on the association of arsenic exposure with hypertension (56-59) or with PRH (14). A study of hypertension in recently pregnant women in Inner Mongolia, China, showed significantly elevated blood

pressure with increasing exposure levels of arsenic (59); however, the study did not assess whether the women had pregnancy-related hypertension or preeclampsia during their pregnancies. A study in Bulgaria found that preeclampsia was significantly more common in pregnant women living near a smelter (exposed to arsenic in air and soil) (14). The incidence of PRH reported on Utah birth certificates in 2000-2002 was 55.7 per 1,000 births, while the incidence of eclampsia was 2.6 per 1,000 births (60).

Stillbirth

Stillbirth is generally defined as fetal death after 20 weeks gestation (61). In Utah, fetal death certificates are required for fetal deaths at 20 or more weeks of gestation. For this study, "stillbirth" is defined as 1) pregnancy loss at 20 weeks gestation or later in Utah recorded on a fetal death certificate, and 2) pregnancy loss where a birth certificate was issued but the 1-minute and 5-minute Apgar scores were both zero. The incidence of stillbirth in Utah is approximately 4.9 per 1,000 live births (51). Stillbirth, as well as spontaneous abortion and neonatal mortality, have been associated with arsenic exposure in several studies (5, 9-13); however, findings have been mixed.

Specific Aims

The specific aims of this study were to: 1) develop estimates of drinking water arsenic concentrations over time for Utah residents (age 18 and older) who delivered a live birth or had a stillbirth in Utah between January 1, 1989, and December 31, 2006, and whose residence was inside the boundaries of a CWS in Utah, and 2) examine the relationship between these exposures and three adverse reproductive outcomes: stillbirth, SGA, and PRH.

Methods and Analysis Process

Steps in the project are listed below; the methods are described in greater detail for each specific outcome in Chapters 2, 3, and 4.

Step 1 – Obtained Data on Maternal Address, Health Outcomes, and Risk Factors

After approval of the study by the Institutional Review Boards of the University of Utah and the Utah Department of Health (UDOH), the UDOH Office of Vital Records and Statistics provided data on maternal address, health outcomes, and risk factors recorded on birth and fetal death certificates for the years 1989 to 2006.

Other sources of data for risk factors included US Geological Survey elevation data (62), Census data for 1990 and 2000 on median family income and median housing value by census block (63), and Rural/Urban Commuting Area (RUCA) data from the US Department of Agriculture (64).

Step 2 – Geocoded Maternal Addresses and Geospatially Mapped Each CWS

The UDOH Environmental Epidemiology program provided geocoded maternal addresses, which were then reviewed to identify and correct errors. Addresses that had not been geocoded were manually geocoded, where possible.

The UDNR provided a spatial database of boundaries for most CWS service areas. Boundaries were updated and refined, and boundaries were added for CWSs not in the database, based on publicly available resources, Utah Department of Environmental Quality (UDEQ) records, and tax area spatial data available from the Utah Automated Geographic Resource Center (62).

Step 3 – Estimated Annual Arsenic Concentrations for Each CWS

The UDEQ provided water quality data from the Safe Drinking Water Information System (SDWIS) that included 27,500 arsenic sample results for the years 1978-2007. These data were used to estimate annual average arsenic concentrations for each CWS. For years where no sample value was reported, sample results were estimated using interpolation and extrapolation.

Step 4 – Linkage of Data

Geocoded maternal addresses were spatially linked to the CWS in which the address was located, and to spatial databases for elevation, census block, and RUCA. Each live birth and stillbirth was then linked to the estimated annual arsenic concentration for the year in which the first trimester of each pregnancy was estimated to have occurred, based on gestational age recorded on vital records. Observations for which no CWS could be assigned were then dropped from further analysis as there was no associated water quality data. At this point in the analysis, maternal addresses and CWS names and numbers were deleted from data files.

Step 5 – Bivariate and Multivariate Analyses

The final step was bivariate and multivariate analyses, including sensitivity analyses and tests for goodness of fit, for each outcome measure.

Summary

The three studies are presented in detail in Chapters 2, 3, and 4, followed by a conclusion (Chapter 5).

References

(1) Agency for Toxic Substances and Diseases Registry. *Toxicological Profile for Arsenic*. Atlanta, GA: Agency for Toxic Substances and Diseases Registry; 2007.

(2) Vahter ME, Li L, Nermell B, et al. Arsenic exposure in pregnancy: a population-based study in Moab, Bangladesh. *J Health Popul Nutr*. 2006;24(2):236-245.

(3) Yang CY, Chang CC, Tsai SS, Chuang HY, Ho CK, Wu TN. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environ Res*. 2003;91(1):29-34.

(4) Zelikoff JT, Bertin JE, Burbacher TM, et al. Health risks associated with prenatal metal exposure. *Fundam Appl Toxicol*. 1995;25(2):161-170.

(5) Engel RR, Smith AH. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. *Arch Environ Health*. 1994;49(5):418-427.

(6) Kwok RK, Kaufmann RB, Jakariya M. Arsenic in drinking water and reproductive health outcomes: a study of participants in the Bangladesh Integrated Nutrition Programme. *J Health Popul Nutr*. 2006;24(2):190-205.

(7) Myers SL, Lobdell DT, Liu Z, et al. Maternal drinking water arsenic exposure and perinatal outcomes in inner Mongolia, China. *J Epidemiol Community Health*. 2010;64(4):325-329.

(8) Aschengrau A, Zierler S, Cohen A. Quality of community drinking water and the occurrence of spontaneous abortion. *Arch Environ Health*. 1989;44(5):283-290.

(9) Nordstrom S, Beckman L, Nordenson I. Occupational and environmental risks in and around a smelter in northern Sweden. I. Variations in birth weight. *Hereditas*. 1978;88:43-46.

(10) Rahman A, Vahter M, Ekstrom EC, et al. Association of arsenic exposure during pregnancy with fetal loss and infant death: a cohort study in Bangladesh. *Am J Epidemiol*. 2007;165(12):1389-1396.

(11) Ahmad SA, Sayed MH, Barua S, et al. Arsenic in drinking water and pregnancy outcomes. *Environ Health Perspect*. 2001;109(6):629-631.

(12) Milton AH, Smith W, Rahman B, et al. Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh. *Epidemiology*. 2005;16(1):82-86.

(13) von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, et al. Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *Am J Epidemiol*. 2006;(163(7):662-669.

(14) Ihrig MM, Shalat SL, Baynes C. A hospital-based case-control study of stillbirths and environmental exposure to arsenic using an atmospheric dispersion model linked to a geographical information system. *Epidemiology*. 1998;9(3):290-294.

(15) Tabacova S, Little RE, Balabaeva L, et al. Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. *Reprod Toxicol*. 1994;8(3):217-224.

(16) Hopenhayn C, Ferreccio C, Browning SR, et al. Arsenic exposure from drinking water and birth weight. *Epidemiology*. 2003;14(5):593-602.

(17) Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, et al. Chronic arsenic exposure and risk of infant mortality in two areas of Chile. *Environ Health Perspect*. 2000;108(7):667-673.

(18) Huyck KL, Kile ML, Mahiuddin G, et al. Maternal arsenic exposure associated with low birth weight in Bangladesh. *J Occup Environ Med*. 2007;49(10):1097-1104.

(19) Borzsonyi M, Bereczky A, Rudnai P, et al. Epidemiological studies on human subjects exposed to arsenic in drinking water in southeast Hungary. *Arch Toxicol*. 1992;66(1): 77-78.

(20) Cherry N, Shaikh K, McDonald C, et al. Stillbirth in rural Bangladesh: arsenic exposure and other etiological factors: a report from Gonoshasthaya Kendra. *Bull World Health Organ*. 2008;86(3):172-177.

(21) National Research Council. *Arsenic in Drinking Water*. National Research Council: Washington, DC; 1999.

(22) National Research Council. *Arsenic in Drinking Water: 2001 Update*. National Research Council: Washington, DC; 2001.

(23) Frost FJ, Muller T, Petersen HV, Thomson B, et al. Identifying US populations for the study of health effects related to drinking water arsenic. J *Expo Anal Environ Epidemiol*. 2003;13(3):231-239.

(24) Pacyna J. Atmospheric emissions of arsenic, cadmium, lead and mercury from high temperature processes in power generation and industry. In: Hutchinson T, Meema K, eds. *Lead, Mercury, Cadmium and Arsenic in the Environment*. New York, NY: John Wiley & Sons; 1987:69-87.

(25) Bencko V. Carcinogenic, teratogenic, and mutagenic effects of arsenic. *Environ Health Perspect*. 1977;19:179-182.

(26) Mead MN. Arsenic: in search of an antidote to a global poison. *Environ Health Perspect*. 2005;113(6):381-386.

(27) Lewis DR, Southwick JW, Scanlan LP, et al. The feasibility of epidemiologic studies of waterborne arsenic: a mortality study in Millard County, Utah. *J Envir Health*. 1998;60(9):14.

(28) Welch AH, Lico MS, Hughes JL. Arsenic in ground water of the western United States. *Ground Wate*r. 1988;26(3):333-347.

(29) Utah Department of Health, Panichello JD. Health Consultation: Arsenic Exposure in Culinary Drinking Water, Millard County, Utah. Agency for Toxic Substances and Disease Registry. 2009. (http://www.atsdr.cdc.gov/hac/pha/ArsenicExposureinMillardCountyUT/ArsenicExposureinUtahHC09-30-2009.pdf) (Accessed February 8, 2011).

(30) Utah Department of Environmental Quality. Drinking water fact sheet. 2007. (http://www.deq.utah.gov/references/FactSheets/Drinking_Water.htm) (Accessed February 22, 2007).

(31) International Agency for Research on Cancer. Some drinking-water disinfectants and contaminants including arsenic. *IARC Monogr Eval Carcinog Risks Hum*. 2004;84:1-477.

(32) Colt JS, Baris D, Clark SF, et al. Sampling private wells at past homes to estimate arsenic exposure: a methodologic study in New England. *J Expo Anal Environ Epidemiol*. 2002; 12(5):329-334.

(33) Utah Department of Natural Resources. Municipal and Industrial Water Use in Utah. December 29, 2010. (http://www.water.utah.gov/Reports/Mandl%20Water%20Use%20in%20Utah.pdf) (Accessed February 9, 2011).

(34) Smith A, Bates M, Steinmaus C. Arsenic epidemiology and drinking water standards. *Science*. 2002;296:2145-246.

(35) Centeno JA, Mullick FG, Martinez L, et al. Pathology related to chronic arsenic exposure. *Environ Health Perspect*. 2002;110(suppl):883-886.

(36) Abernathy CO, Thomas DJ, Calderon RL. Health effects and risk assessment of arsenic. *J Nutr*. 2003;133(suppl):1536S-1538S.

(37) Bates MN, Smith AH, Cantor KP. Case-control study of bladder cancer and arsenic in drinking water. *Am J Epidemiol*. 1995;141(6):523-530.

(38) Navas-Acen A, Silbergeld EK, Pastor-Barriuso R, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA*. 2008;300(7):814-822.

(39) Smith AH, Lingas EO, Rahman M. Contamination of drinking-water by arsenic in Bangladesh: a public health emergency. *Bull World Health Organ*. 2000;78(9):1093-1103.

(40) Frisbie SH, Ortega R, Maynard DM, et al. The concentrations of arsenic and other toxic elements in Bangladesh's drinking water. *Environ Health Perspect*. 2002;110(11):1147-1153.

(41) Meliker JR, Wahl RL, Cameron LL, et al. Arsenic in drinking water and cerebrovascular disease, diabetes mellitus, and kidney disease in Michigan: a standardized mortality ratio analysis. *Environ Health*. 2007;6:4. (http://www.ehjournal.net/content/6/1/4) (Accessed November 3, 2009).

(42) Concha G, Vogler G, Lezcano D, et al. Exposure to inorganic arsenic metabolites during early human development. *Toxicol Sci*. 1988;44(2):185-190.

(43) Ferm VH. Arsenic as a teratogenic agent. *Environ Health Perspect*. 1977;19:215-217.

(44) Shalat SL, Walker DB, Finnell RH. Role of arsenic as a reproductive toxin with particular attention to neural tube defects. *J Toxicol Environ Health*. 1996;48(3):253-272.

(45) Fangstrom B, Moore S, Nermell B, et al. Breast-feeding protects against arsenic exposure in Bangladesh infants. *Environ Health Perspect*. 116(7):963-969.

(46) California Environmental Protection Agency. Evidence on developmental and reproductive toxicity of inorganic arsenic. (http://www.oehha.ca.gov/Prop65/AS-HID.pdf) (Accessed October 15, 2008).

(47) Tseng CH, Chong CK, Chen CJ, et al. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis*. 1996;120(1-2):125-133.

(48) Chiou HY, Huang WI, Su CL, et al. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke*. 1997;28(9):1717-1723.

(49) Wang CH, Jeng JS, Yip PK, et al. Biological gradient between long-term arsenic exposure and carotid atherosclerosis. *Circulation*. 2002;105(15):1804-1809.

(50) Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. *J Nutr*. 2003;133(suppl):1592S-1596S.

(51) Kramer MS, Oliveier M, McLean EH, et al. The impact of intrauterine growth retardation and body proportionality on fetal and neonatal outcome. *Pediatrics*. 1990;85:707-713.

(52) Torrance HL, Voorbij HA, Wijnberger LD, et al. Lung maturation in small for gestational age fetuses from pregnancies complicated by placental insufficiency or maternal hypertension. *Early Hum Dev*. 2008;84(7):465-469.

(53) Reynolds C, Mabie WC, Sibai BM. Hypertensive States of Pregnancy. In: *Current Obstetric & Gynecologic Diagnosis & Treatment. 9th Edition*. DeCherney AH, Nathan L, eds. New York, NY; McGraw Hill; 2003:338-353.

(54) Thadhani R, Solomon CG. Preeclampsia – a glimpse into the future? *N Engl J Med*. 2008;359(8):858-860.

(55) Cunningham F, Lindheimer M. Hypertension in pregnancy. *N Engl J Med*. 1992;326:927-932.

(56) Kwok RK, Mendola P, Liu ZY, et al. Drinking water arsenic exposure and blood pressure in healthy women of reproductive age in Inner Mongolia, China. *Toxicol Appl Pharmacol*. 2007;222(3):337-343.

(57) Chen CJ, Hsueh YM, Lai MS, et al. Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension*. 1995;25:53-60.

(58) Rahman M, Tondel M, Ahmad SA, et al. Hypertension and arsenic exposure in Bangladesh. *Hypertension*. 1999;33:74-78.

(59) Kwok RK, Mendola P, Liu ZY. Changes in blood pressure during pregnancy associated with drinking water arsenic exposure in Inner Mongolia, China. *Ann Epidemiol*. 2004;14(8):621-624.

(60) Utah Department of Health. Utah Vital Statistics: Quarterly Report, Fourth Quarter 2003. (http://health.utah.gov/vitalrecords/pub_vs/QtrlyData/4thqtr2003.pdf) (Accessed November 3, 2009).

(61) Centers for Disease Control and Prevention. Stillbirth. (http://www.cdc.gov/ncbddd/bd/stillbirths.htm) Accessed February 14, 2011.

(62) Utah Automated Geographic Reference Center. Utah SGID: Vector GIS Data Layers, By Category. Utah GIS Portal. (http://agrc.its.state.ut.us) (Accessed September 10, 2008).

(63) US Census Bureau, American FactFinder. (http://factfinder.census.gov) (Accessed November 10, 2010).

(64) US Department of Agriculture, Economic Research Service. Rural-Urban Commuting Area Codes. (http://www.ers.usda.gov/Data/ RuralUrbanCommutingAreaCodes/) (Accessed September 18, 2010).

CHAPTER 2

ARSENIC IN COMMUNITY DRINKING WATER SYSTEMS AND SMALL FOR GESTATIONAL AGE BIRTH

Abstract

Exposure to arsenic in drinking water has been associated with several adverse birth outcomes. Few studies, however, have investigated the relationship between arsenic exposure via drinking water and birth weight, and the results have been inconsistent. Most of these studies took place in areas with high levels of arsenic. The purpose of this study was to investigate the relationship of low to moderate levels of arsenic in drinking water with small for gestational age (SGA) birth. This study included 631,375 births to Utah residents from 1989 to 2006. Gestational age data from birth certificates were used to identify SGA births based on the 10th percentile birth weight by sex for each week of gestation (22 to 44 weeks). Maternal addresses, as recorded on birth certificates, were geocoded and spatially linked to georeferenced data layers of 476 Community Water System (CWS) service areas statewide and to elevation. Births to women who did not reside within a CWS service area, multiple births, and infants with birth defects were excluded. Water quality data collected for regulatory purposes were used to estimate annual average arsenic levels for each CWS, and these values were assigned to each birth based on the conception year and the CWS providing drinking water to the residence. There were small but statistically significant associations between arsenic concentration and SGA. Using <2.5 µg/L as the referent, the adjusted odds ratio (aOR) for SGA was 1.04, (95% confidence interval (CI) 1.00, 1.07) when arsenic levels were 5.1 to 9.9 µg/L (p-value 0.03), aOR of 1.07 (CI 1.03, 1.12) when levels were 10 µg/L or greater (p-value 0.002). At arsenic levels from 2.5 to 5 µg/L, there was a small, but not statistically significant,

increase in SGA (aOR 1.01, CI 0.98, 1.04). In addition, the frequency of SGA increased with every 1,000 feet (ft) increase in elevation. Compared with births at elevations less than 3,000 ft, the adjusted odds ratio (aOR) for SGA increased with every 1,000 ft gain in elevation, to an aOR of 1.90 (CI 1.64, 2.19) for women residing above 6,000 ft.

Introduction

Arsenic is a naturally occurring metalloid that primarily enters drinking water sources through erosion and dissolution of rocks and minerals (1). Groundwater arsenic levels vary across the United States (US), with higher levels found in many areas of the western states. In Utah, weathering of volcanic rocks and erosion of slag and soil from past mining activities are the major sources of arsenic in groundwater (2, 3). Arsenic levels in drinking water vary greatly throughout Utah, ranging from below the limit of detection to over 400 micrograms per liter (µg/L) in some private wells (4, 5).

Humans are exposed to arsenic through intake of food, water, air, and incidental ingestion of contaminated soil (6). Arsenic in drinking water is in the inorganic form, which is more toxic than the organic form of arsenic generally found in foods. As such, exposure to arsenic via ingestion of drinking water is of primary concern (7). In 2001, the US Environmental Protection Agency (EPA) adopted a new standard (effective January 2006) that arsenic levels in drinking water in community water systems (CWSs) not exceed 10 µg/L, replacing the previous maximum contaminant level (MCL) of 50 µg/L (6).

Chronic exposure to arsenic has consistently been associated with increased incidence of cancers, diseases such as Blackfoot disease, and type II diabetes (5, 8-11). The evidence linking arsenic exposure with lower birth weight and other adverse birth outcomes has been less consistent. Studies in Chile, Taiwan, and Bangladesh each found significant decreases in birth weight in areas with arsenic levels in drinking water higher than 40 µg/L, compared with areas where arsenic was below detection levels (BD) (12-14). A study in Bangladesh found higher prenatal urinary arsenic levels associated with lower birth weight and smaller head and chest circumference in full-term infants (15). In contrast, a third study in Bangladesh compared

exposures ranging from BD to over 300 µg/L and found no association between arsenic and birth weight (16), while a study in China found high arsenic levels in drinking water (>100 µg/L compared to levels <20 µg/L) to be associated with a 0.5 kilogram increase in birth weight (17).

There are no well-defined biological mechanisms to explain the adverse effects of arsenic exposure on fetal growth; however, several modes of effect have been suggested (18). Vascular endothelial cells are suspected to be primary targets of arsenic toxicity (19), and studies have shown a dose-response relationship between arsenic in drinking water and peripheral vascular disease, cerebrovascular disease, and carotid atherosclerosis (20-22). As arsenic readily crosses the placental barrier (6, 23) and has been associated with these vascular effects, it is possible that arsenic may lead to some type of placental abnormality, placental insufficiency, or decreased blood flow, any of which may affect fetal growth (13).

Small for gestational age (SGA) is generally defined as an infant whose weight at birth is less than the 10th percentile for gestational age. It is considered to be a better measure of intrauterine growth restriction (IUGR) than birth weight, as it is based on both birth weight and gestational age. Severely growth-restricted fetuses are at increased risk for stillbirth and neonatal mortality (24). The purpose of this study was to investigate the association between maternal exposure to low to moderately elevated levels of arsenic in drinking water and the risk of SGA birth in a large, well-characterized cohort.

Methods

Study Design and Study Population

This is a retrospective cohort study of SGA births to Utah residents, ages 18 or older, who gave birth between January 1, 1989, and December 31, 2006, in Utah, and whose residence was provided tap water by a CWS. See Table 2.1 for maternal demographic data. A CWS provides water to at least 15 residential service connections or at least 25 people year-round (25). CWSs are regulated under the Safe Drinking Water Act (SDWA) which requires, among other things, regular monitoring of water quality.

Table 2.1 Maternal Demographics, SGA Study, Utah, 1989-2006

	Total#	%	#SGA*	%SGA*
Age				
18-19	39,041	6.2%	5,799	14.9%
20-24	203,202	32.2%	23,025	11.3%
25-29	208,342	33.0%	19,071	9.2%
30-34	123,406	19.6%	10,094	8.2%
>34	57,384	9.1%	4,800	8.4%
Race				
Black	4,229	0.7%	819	19.4%
Native American	6,983	1.1%	763	10.9%
White	597,026	95.1%	58,137	9.7%
Other races	19,441	3.1%	2,673	13.8%
Hispanic				
Yes	67,990	10.8%	8,260	12.2%
No	561,651	89.2%	54,339	9.7%
Education				
<12 years	73,626	11.8%	11,293	15.3%
12 years	204,804	32.8%	22,671	11.1%
>12 years	345,140	55.4%	27,940	8.1%
First pregnancy				
Yes	184,718	29.4%	22,583	12.2%
No	442,957	70.6%	39,796	9.0%
Marital status				
Married	539,039	85.4%	48,816	9.1%
Unmarried	92,335	14.6%	13,973	15.1%
Previous SGA				
Yes	2,803	0.4%	797	28.4%
No	628,572	99.6%	61,992	9.9%
Smoking during pregnancy				
Yes	49,829	7.9%	10,924	21.9%
No	581,546	92.1%	51,865	8.9%
Alcohol during pregnancy				
Yes	8,499	1.4%	1,514	17.8%
No	619,553	98.6%	60,897	9.8%
Pre-pregnancy BMI				
Lowest	41,078	7.1%	7,124	17.3%
Normal	352,509	60.9%	35,446	10.1%
Overweight	112,042	19.4%	8,,942	8.0%
Obese	73,329	12.7%	5,582	7.6%
Weight gain for BMI				
Recommended	252,449	40.0%	25,162	10.0%
Low gain	147,725	23.4%	22,392	15.2%
High gain	231,201	36.6%	15,235	6.6%
Elevation at maternal residence				
<3,000 ft	3,707	0.6%	260	7.0%
3,000-4,000 ft	5,028	0.8%	397	7.9%
4,000-5,000 ft	554,407	87.8%	54,333	9.8%
5,000-6,000 ft	57,541	9.1%	6,429	11.2%
>6,000 ft	10,585	1.7%	1,359	12.8%

Table 2.1 continued

	Total#	%	#SGA*	%SGA*
Metropolitan	522,640	82.8%	50,568	9.7%
Metropolitan adjacent	42,144	6.7%	4,543	10.8%
Small town	39,565	6.3%	4,594	11.6%
Rural	27,022	4.3%	3,084	11.4%

* SGA defined as 10^{th} percentile birth weight at gestational weeks 22-44 based on Utah births in 1989-2006 included in study.

Birth certificate data were obtained from the Utah Department of Health (UDOH) Office of Vital Records and Statistics upon approval from the Institutional Review Boards of the UDOH (Project #226) and the University of Utah (Project #00023217).

SGA was defined as an infant whose weight at birth is less than the 10th percentile, stratified by sex, for each week of gestational age (weeks 22 to 44), based on the distribution of birth weight and gestational age reported on Utah birth certificates during the study time period (Table 2.2). Gestational age recorded on the birth certificate was determined by the birth attendant based on available data such as last menstrual period, prenatal visits, ultrasound data, and/or newborn examination. The sample size for analysis was 631,375 births (Figure 2.1).

Multiple births and infants with birth defects were excluded, as were infants with non-plausible birth weights (<250 grams or >6,000 grams), assumed to be errors in recording. Infants with a recorded gestational age of less than 22 weeks were excluded, as births prior to 22 weeks are rarely viable, and infants with a gestational age greater than 44 weeks were excluded, as births are usually induced by 44 weeks gestation (Figure 2.1). Births were also excluded from the study if a) birth weight and/or gestational age were not reported on the birth certificate; b) no address was reported on the birth certificate; c) the address was outside of a CWS service area; d) address information was inadequate to identify whether the maternal address at the time of birth was within the boundaries of a CWS; e) the address was within the service area of a CWS on tribal lands, but water quality data were not available; f) the mother was not a Utah resident; g) the birth was not in Utah; and h) if the birth occurred in 1990, as addresses were not available electronically for that year. Of the 725,014 Utah births to women age 18 or older in 1989-2006, 93,639 (12.9%) were excluded from the study.

Exposure Assignment

Tap water arsenic concentrations for each birth were based on arsenic concentrations reported to the Utah Department of Environmental Quality (UDEQ) by the CWS that served the maternal address listed on the birth certificate during the year of the birth.

Table 2.2 Births by Gestational Age, SGA 10th Percentile Counts, and Weight Thresholds by Sex in Utah, 1989-2006

Gestation Week	Births	SGA 10th percentile #SGA	#Male	#Female	SGA weight threshold (grams) Male	Female
22	151	14	8	6	420	400
23	202	19	10	9	485	430
24	259	23	13	10	510	468
25	289	27	14	13	600	539
26	359	33	19	14	680	579
27	412	40	23	17	750	645
28	520	50	29	21	852	810
29	642	61	32	29	964	879
30	860	85	48	37	1,115	1,029
31	1,154	115	65	50	1,270	1,234
32	1,748	174	97	77	1,484	1,385
33	2,800	279	157	122	1,685	1,637
34	5,280	526	298	228	1,949	1,835
35	9,748	972	528	444	2,103	2,085
36	21,974	2,162	1,172	990	2,410	2,296
37	51,140	5,084	2,714	2,370	2,623	2,520
38	123,595	12,354	6,398	5,956	2,827	2,715
39	200,071	19,987	10,140	9,847	2,974	2,857
40	139,821	13,898	6,941	6,957	3,060	2,940
41	51,267	5,013	2,439	2,574	3,090	2,980
42	12,267	1,205	599	606	3,033	2,920
43	4,500	450	220	230	2,929	2,847
44	2,234	218	105	113	2,920	2,850
Total	631,375	62,789	32,069	30,720		

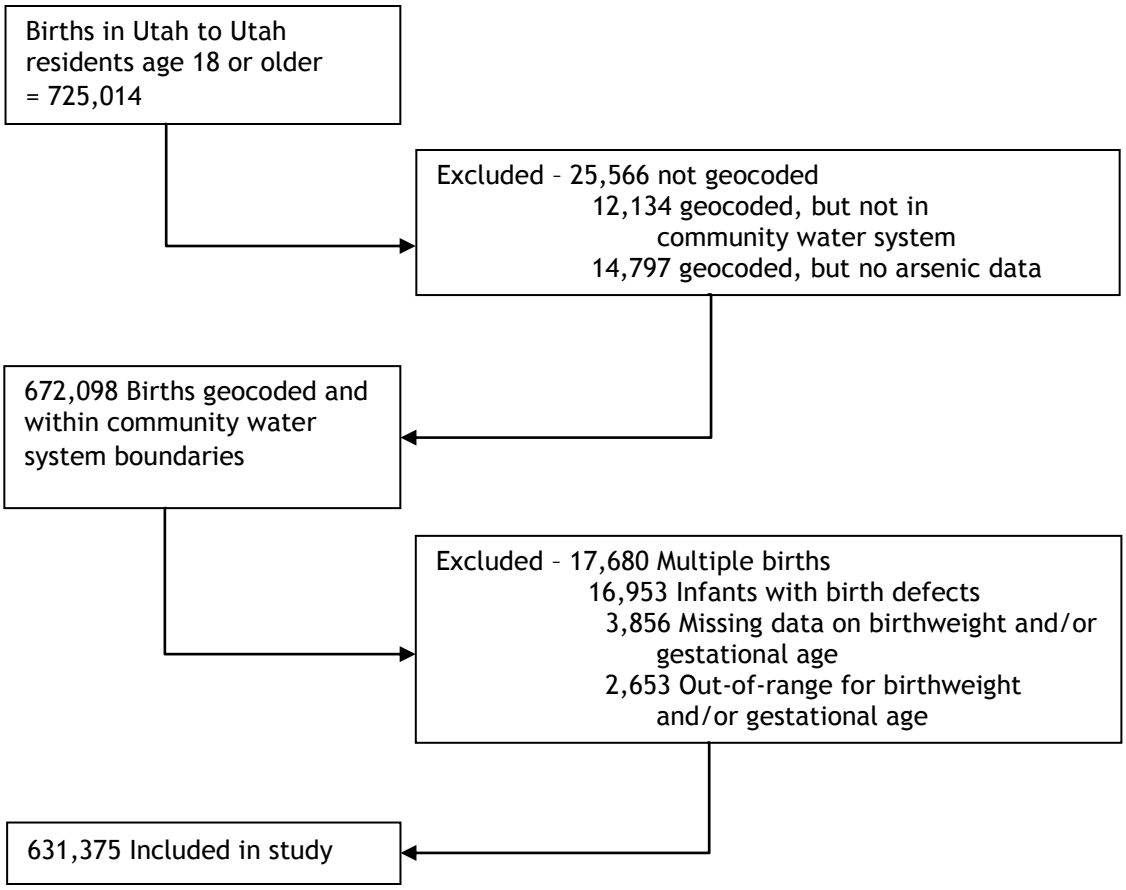

Figure 2.1 SGA Exclusion and Inclusion Criteria, Utah, 1989-2006

The UDOH provided geocoded coordinates for many of the addresses. We reviewed these results to identify and correct errors. Addresses that had not been geocoded by UDOH were manually geocoded to specific addresses where possible using ArcGIS® 9.3 (ESRI, Redlands, CA). Where only the city and zip code were available, but the mother indicated she lived within the city limits: 1) the residence was geocoded to the center of the city (if only one CWS provided service in that city); or 2) the residence was geocoded to the zip code delivery centroid within the city limits (if more than CWS provided service within the city). Where there was no street address (or the address was a post office box) and the mother indicated that she lived outside the city limits, the mother was assumed to live outside the limits of the CWS service area and was, therefore, excluded.

Over 97% of the maternal addresses in each county were geocoded with sufficient precision to determine their location inside or outside of specific CWS service areas.

Each geocoded residential address was linked spatially to a CWS based on the reported boundaries of the CWS service area. The Utah Department of Natural Resources (UDNR) provided a spatial database of most of the CWS boundaries statewide. Many of the boundaries, however, were not based on legal descriptions, did not include water systems regulated by the Utah Public Utilities Commission, and did not include systems that had closed prior to 2007. The service areas for each water system were reviewed and updated using water system maps; legal descriptions of boundaries; UDEQ records on mergers, changes in boundaries, ownership, system names, and/or CWS numbers; and tax area boundaries (water systems, subdivisions, and municipalities) provided by the Utah Automated Geographic Reference Center (26). Records from the UDEQ were of particular importance for mapping CWSs that had closed at some point during the study time period and had not been mapped by other agencies. CWS boundaries and subdivision plat maps were also obtained through on-line searches of websites for county assessors, subdivisions, and municipalities. When questions remained regarding service area boundaries, water systems were contacted by phone and/or in person to verify or delineate service area boundaries.

Where different water sources clearly served specific areas of a CWS service area and these sources had significantly different arsenic levels, the service area was divided into regions that were treated as independent service areas.

Through this process we identified and developed boundaries for 58 CWSs that were not in the original UDNR database, and made modifications to over two-thirds of the CWS boundaries we had obtained from the various sources. The 12 water systems that are/were wholesalers to other CWSs and did not directly provide water to any residential connections were not mapped. We were unable to find information on service area boundaries and water quality data for 13 closed, small water systems, so these systems were also not mapped. Areas served by tribal water systems (who reported sample data to the US EPA and not to the UDEQ) were excluded from this study, except for those years where water quality data was available on-line for tribal systems.

Water quality data from the Safe Drinking Water Information System (SDWIS) for Utah water systems from 1978–2006, including 27,500 arsenic sample results, were provided by the UDEQ. We used this database to identify the specific water system (and/or wholesale water system) and sample data for each exposure year for which sample data had been reported to the UDEQ. While some CWSs had consistent water sources for the entire time period, others supplied groundwater or surface water from local sources in some years but became purchasers in later years due to regional consolidation or to improve water quality. We used these data to estimate annual average arsenic concentrations for each CWS. When there was no sample result for a given year in the time period that the CWS was providing service, we used linear interpolation or extrapolation.

Many CWSs blend water from various groundwater and/or surface water sources that may have very different arsenic levels. In such cases all results from each source in a given year were first averaged, and the average values for each source were then averaged across all sources for that CWS in that year. Some water sources are only used seasonally; however, data on the production from each source and the number of days the source was utilized were not available. As the relative contribution from each of the water sources could not be estimated,

all sources were assumed to have contributed equally. Data from wells classified as 'inactive' in the UDEQ dataset were not used, except in those cases where the date that the well became inactive was available.

Within each CWS, reported arsenic levels were generally consistent across time. The greatest variability was seen in results reported as BD, as reported detection limits ranged from 0 to 50 µg/L. These differences in detection limits were primarily due to changes in reporting requirements over time, but were also due to the use of different laboratories within the same time periods.

Where a system reported that a sample value was BD, we generally assigned the sample a value of half of the censoring level. Where detection limits were reported as greater than the current maximum contaminant level (MCL) (10 µg/L), we reviewed the sample values for the source in later years, as well as the general arsenic levels from similar sources in the immediate area to determine the appropriate value to assign to that sample. A few groundwater systems, for example, had consistently low levels of arsenic for most years (<2.5 µg/L), but reported a few BD results as having a detection level of 50 µg/L. Where a BD was reported as 50 µg/L in a system where all other sources and all other years of sampling were very low, assigning a value of 25 µg/L would result in an estimated arsenic concentration over twice the current MCL. In these instances we reviewed the UDEQ records and Consumer Confidence Reports (CCRs) for the systems and assigned an arsenic sample value that more accurately represented arsenic levels for that year for that CWS.

All annual sample values assigned to each system were coded to identify whether the annual value was based on all samples having specific detection values, or all samples being BD values, or samples with a mix of specific and BD values, or an annual value that was adjusted based on review of UDEQ records and/or CCRs. To address these differences in precision of reporting levels, as well as the potential error in assigning values by time trends based on the 3-year reporting cycles, we conducted sensitivity analyses.

Each birth was then linked to the estimated annual average arsenic concentration for the CWS providing service to the maternal address during the first trimester of the pregnancy,

based the gestational age reported on the birth certificate. Because of the known relationship between elevation of residence and decrease in birth weight (27-29), births were also linked to a digital elevation model (90 meter grid) from the US Geologic Survey (30). Births were also linked to median income and median housing values for the census block group for 1990 and 2000 (31), and Rural-Urban Commuting Area Codes for 1990 and 2000, based on the location of the maternal residence (32). Births that occurred before 1995 were assigned the value associated with 1990, while births from 1995 on were assigned the value associated with the year 2000.

Analytical Approach

The individual births are the units of analysis for this study. The relationship between levels of arsenic in drinking water and the birth outcomes were assessed using bivariate analyses and multivariate logistic regression. The measure of effect was the relative risk for each outcome, adjusted for potential confounders. Statistical Analysis Systems software, version 9 (SAS, Cary NC) and Stata version 10 (Stata Corporation, College Station, TX) were used for data reduction and statistical analyses.

We examined the distributions of the health outcomes and covariates, examined the relationships between the covariates to identify potential collinearity, and assessed the bivariate relationships between risk factors and SGA. Covariates were identified as potential confounders if they were associated with both arsenic exposure and SGA at a significance level of p-value < 0.2 in bivariate analyses. Potential confounders and known risk factors were included in the initial main effects models. Risk factors that have been associated with SGA that were assessed in initial models included maternal age, low maternal weight gain, low pre-pregnancy weight, previous SGA, smoking, alcohol use, maternal height, elevation at maternal residence, maternal race/ethnicity, chronic hypertension, parity, pregnancy related hypertension, renal disease, and socioeconomic status. Proxy measures that were used for socioeconomic status were years of education, and the median income and median housing values for the mother's census block group (based on 1990 and 2000 Census data) (31).

Elevation was categorized into 1,000 foot intervals. Arsenic concentration was assessed both as a continuous variable and as a categorical variable. We conducted sensitivity analyses to assess the effects of our assumptions in creating annual average concentrations on the resulting associations with SGA. Finally, interaction terms were tested for significant covariates that previous studies or etiology suggested had the potential for effect modification.

Stepwise procedures, followed by diagnostic tests, including likelihood ratio tests, were used to assess significance and goodness-of-fit after the addition of each covariate. The statistical significance of the estimated parameters was assessed using two-sided tests with an alpha of 0.05.

Results

Compared with arsenic levels less than 2.5 µg/L, there was a small but statistically significant increase in SGA for arsenic levels at 5.1-9.9 µg/L, with an adjusted odds ratio (aOR) of 1.04, 95% confidence interval (CI) 1.00, 1.07 (p-value 0.03); and at levels 10 µg/L or greater, with an aOR of 1.07, 95% CI: 1.03, 1.12 (p-value 0.002). At arsenic levels from 2.5-5 µg/L, there was a small, but not statistically significant, increase in SGA with an aOR of 1.01 (CI 0.99, 1.04). Over 87% of the arsenic exposure levels were 5 µg/L or less. The median exposure level in the highest arsenic category was 11.7 µg/L (mean 13.0 µg/L). Only 142 of the maternal residences (0.02% of the study population) were in CWS service areas that had estimated arsenic levels greater than 40 µg/L; the highest exposure level was 126.1 µg/L.

Because a dose-effect association might be more pronounced in newborns that are more severely growth restricted, we repeated the analysis using a gender-specific birthweight-gestational age calculation at the 5^{th} percentile (n=31,387). The association between arsenic and SGA was somewhat stronger in these infants; compared with arsenic at levels <2.5 µg/L, the aOR for 2.5-5.0 µg/L was 1.05, 95% CI 1.01, 1.09 (p-value 0.01); the aOR for 5.1 to 9.9 µg/L was 1.08, 95% CI 1.03, 1.13 (p-value 0.001); and the aOR for levels of 10 µg/L or greater was 1.09, 95% CI 1.03, 1.16 (p-value 0.004).

As arsenic levels were interpolated for years when sampling was not required and/or was not reported to UDEQ, we repeated the analysis first excluding interpolated values, and then excluding all BD values. In each of the follow-up analyses, increased arsenic levels were significantly associated with increased rates of SGA, and the aORs were essentially the same.

See Table 2.3 for the covariates included in the final model. The majority of the residences were in urban areas (83%) and were at less than 5,000 feet elevation. Over 55% of the population had more than 12 years education, and over 37% of the mothers were age 18–24. The racial distribution differed from the US population (2000 Census), with 95.1% White (compared with 75.1% US) and 0.7% Black (compared with 12.3% US) (31). The study population was 10.8% Hispanic, compared with 12.5% US. Less than 9% of the women reported smoking, compared with the 23% national estimate in 2000 (33).

The frequency of SGA increased with every 1,000 feet increase in elevation, controlling for the covariates. Women residing above 6,000 feet had almost twice the risk of a having an SGA baby as compared to women residing below 3,000 feet (aOR 1.90, CI 1.64, 2.19). Even women living at moderate elevations, where the major population centers are situated (elevation 4,000 to 5,000 ft), were 1.37 times more likely to have an SGA baby than women residing at lower elevations (95% CI 1.20, 1.56).

As expected, risk of SGA was significantly higher for women with lower body mass index (BMI), women less than 5 feet tall, for those with lower weight gain than recommended for their BMI, for those who reported smoking or alcohol use during pregnancy, and for women with less than 12 years education. Women who had an SGA birth were three times as likely to have had a previous SGA birth as women who did not have an SGA birth (CI 3.06, 3.69). Risks were increased in non-White races, and in women with placenta previa, abruptio placenta, pregnancy-related hypertension, and/or chronic hypertension.

There was a significant interaction between mother's age and parity. Of births to women age 18-19, 14.9% were SGA, with overall rates decreasing with increasing age; only 8.2%-8.4% of the births to women over age 29 were SGA. SGA risk was also higher in nulliparous women; 12.2% of first pregnancies were SGA compared with 9.0% in multiparous women.

Table 2.3 Risk Factors for Population-Specific SGA Included in Final Model, Utah, 1989-2006

	Total #	%	#SGA*	%SGA*	aOR	95% CI
Arsenic in Drinking Water						
<2.5 µg/L (ref)	466,658	73.9%	45,868	9.8%		
2.5-5.0 µg/L	88,663	14.0%	8,755	9.9%	1.01	(0.99, 1.04)
5.1-9.9 µg/L	52,710	8.4%	5,645	10.7%	1.04	(1.00, 1.07)
>9.9 µg/L	23,344	3.7%	2,521	10.8%	1.07	(1.03, 1.12)
Elevation at maternal residence						
<3,000 ft (ref)	3,707	0.6%	260	7.0%		
3,000-4,000 ft	5,028	0.8%	397	7.9%	1.08	(0.91, 1.28)
4,000-5,000 ft	554,407	87.8%	54,333	9.8%	1.37	(1.20, 1.56)
5,000-6,000 ft	57,541	9.1%	6,429	11.2%	1.60	(1.40, 1.83)
>6,000 ft	10,585	1.7%	1,359	12.8%	1.90	(1.64, 2.19)
Smoking during pregnancy						
Yes	49,829	7.9%	10,924	21.9%	2.46	(2.39, 2.53)
No (ref)	581,546	92.1%	51,865	8.9%		
Maternal Race						
Black	4,229	0.7%	819	19.4%	1.92	(1.77, 2.10)
Native American	6,983	1.1%	763	10.9%	1.03	(0.95, 1.12)
White (ref)	597,026	95.1%	58,137	9.7%		
Other races	19,441	3.1%	2,673	13.8%	1.44	(1.38, 1.51)
Hispanic						
Yes	67,990	10.8%	8,260	12.2%	1.09	(1.06, 1.12)
No (ref)	561,651	89.2%	54,339	9.7%		
Previous SGA						
Yes	2,803	0.4%	797	28.4%	3.37	(3.06, 3.69)
No (ref)	628,572	99.6%	61,992	9.9%		
Maternal age						
18-19	39,041	6.2%	5,799	14.9%	1.17	(1.11, 1.25)
20-24	203,202	32.2%	23,025	11.3%	1.11	(1.08, 1.15)
25-29 (ref)	208,342	33.0%	19,071	9.2%		
30-34	123,406	19.6%	10,094	8.2%	0.93	(0.91, 0.96)
>34	57,384	9.1%	4,800	8.4%	0.96	(0.92, 1.00)
Pregnancy-related hypertension						
Yes	31,527	5.0%	4,934	15.7%	2.10	(2.03, 2.17)
No (ref)	599,848	95.0%	57,855	9.6%		
Chronic hypertension						
Yes	3,081	0.5%	434	14.1%	1.75	(1.56, 1.96)
No (ref)	628,294	99.5%	62,355	9.9%		
Mother less than 5 feet tall						
Yes	72,489	11.5%	9,980	13.8%	1.81	(1.75, 1.88)
No (ref)	558,886	88.5%	52,809	9.5%		
Weight gain for BMI						
Recommended	252,449	40.0%	25,162	10.0%		
Low gain	147,725	23.4%	22,392	15.2%	1.60	(1.57, 1.63)
High gain	231,201	36.6%	15,235	6.6%	0.61	(0.59, 0.62)
First pregnancy						
Yes	184,718	29.4%	22,583	12.2%	1.60	(1.55, 1.66)
No (ref)	442,957	70.6%	39,796	9.0%		
Pre-pregnancy BMI						
Lowest	41,078	7.1%	7,124	17.3%	1.51	(1.46, 1.55)
Normal	352,509	60.9%	35,446	10.1%		
Overweight	112,042	19.4%	8,,942	8.0%	0.88	(0.86, 0.90)
Obese	73,329	12.7%	5,582	7.6%	0.73	(0.71, 0.76)

Table 2.3 continued

	Total #	%	#SGA*	%SGA*	aOR	95% CI
Abruptio placenta						
Yes	6,767	1.1%	1,066	15.8%	1.45	(1.35, 1.57)
No (ref)	624,608	98.9%	61,723	9.9%		
Placenta previa						
Yes	2,401	0.5%	307	12.8%	1.28	(1.12, 1.47)
No (ref)	628,974	99.5%	62,482	9.9%		
Education						
<12 years	73,626	11.8%	11,293	15.3%	1.12	(1.08, 1.15)
12 years (ref)	204,804	32.8%	22,671	11.1%		
>12 years	345,140	55.4%	27,940	8.1%	0.83	(0.81, 0.85)
Marital status						
Married I(ref)	539,039	85.4%	48,816	9.1%		
Unmarried	92,335	14.6%	13,973	15.1%	1.15	(1.12, 1.18)
Alcohol during pregnancy						
Yes	8,499	1.4%	1,514	17.8%	1.18	(1.10, 1.27)
No	619,553	98.6%	60,897	9.8%		
Age-First Pregnancy Interaction						
Age<20, first pregnancy	26,685	69.2%	3,987	14.8%	0.74	(0.69, 0.81)
Age<20, not first	11,942	30.8%	1,781	14.9%		
Age 20-24, first pregnancy	94,167	46.6%	10,966	11.7%	0.82	(0.78, 0.86)
Age 20-24, not first	107,952	53.4%	11,922	11.0%		
Age 25-29, first pregnancy	46,319	22.4%	5,330	11.5%		
Age 25-29, not first	160,844	77.6%	13,618	8.5%		
Age 30-34, first pregnancy	13,010	10.6%	1,671	12.8%	1.18	(1.10, 1.27)
Age 30-34, not first	109,600	89.4%	8,334	7.6%		
Age >34, first pregnancy	4,337	7.6%	629	14.5%	1.28	(1.15, 1.42)
Age >34, not first	52,619	92.4%	4,141	7.9%		

* SGA defined as 10th percentile birth weight at gestational weeks 22-44 based on Utah births in 1989-2006 included in study.

In nulliparous women over age 34, however, 14.5% of births were SGA, compared with 7.9% of births to multiparous women over age 34. In nulliparous women ages 30-34, 12.8% of births were SGA, compared with 7.6% of births to multiparous women ages 30-34. In women ages 18-24, SGA rates in nulliparous women were comparable to those of multiparous women. SGA rates were highest in nulliparous women ages 18-19 and in those older than age 34.

The overall mean arsenic levels for 1989-2006, source (surface or groundwater), and location (metropolitan or nonmetropolitan) for the 476 CWSs included in the study are shown in Table 2.4. A higher proportion of CWSs that relied on groundwater (7%) had an average concentration of 10 µg/L or greater compared with systems supplied primarily by surface water (2%). Water systems serving the urban core had somewhat lower levels of arsenic.

Discussion

After adjusting for multiple potential confounders and other risk factors for SGA, arsenic was associated with a small, but statistically significant, increased risk of SGA. While the effect levels are modest, the ability to control for a large number of potential confounders and known risk factors reduces the chance that these results are due to uncontrolled confounding. In addition, the large sample size and substantial gradient of arsenic exposure levels allowed us to demonstrate moderately small, but statistically significant, effects.

This is one of the first studies to examine the relationship of arsenic in drinking water to SGA births. Six studies that examined the association of arsenic with lower birth weight had disparate results; four studies found arsenic to be a significant risk factor for lower birth weight, one found no association, and the remaining study found arsenic exposure to be a protective factor (11-15). While the effect estimates in the studies that did find an association were larger than those found in this study, the upper exposure levels were much higher as well (50–400 µg/L).

We also found a strong relationship between elevation and the risk of SGA birth, consistent with past studies. To our knowledge, this is one of the first studies, however, to demonstrate a significant increase in SGA risk with relatively small increases in elevation

Table 2.4 Overall Mean Arsenic Concentrations (1989-2006) by Community Water System Attributes in Utah

Arsenic mean 1989-2006	CWS		Primarily Surface Water		Primarily Groundwater		Metropolitan		Non-Metropolitan	
µg/L	#	%	#	%	#	%	#	%	#	%
<2.5	290	61%	69	76%	221	57%	86	72%	204	57%
2.5-5	116	24%	16	18%	100	26%	21	18%	95	27%
5.1-9.9	43	9%	4	4%	39	10%	8	7%	35	10%
>9.9	27	6%	2	2%	25	6%	5	4%	22	6%
Total	476		91		385		120		356	

(1,000 ft). Elevation was also more accurately assigned since it was determined by residential address and not by county or census block location. Increased rates of SGA at high altitude are generally attributed to chronic hypoxia; however, the mechanisms by which hypoxia acts to reduce fetal growth are not well understood (27-29).

There were statistically significant relationships between many of the known risk factors and SGA, and the observed associations were as expected. Of particular interest was the modification of the effect of age depending on parity. Although SGA risk was lowest in women age 30 and above and highest in those under age 25, SGA risk was highest in nulliparous women older than 34 and lowest in women younger than 25.

SGA was increased in Hispanics and certain racial groups; however, this increase may be due to the much higher frequency of short stature. Many of these infants, though technically classified as SGA, may be an appropriate weight for gestational age due to the height of the mother and race/ethnicity.

The most significant limitations of this study are related to arsenic exposure assignment. As this was a retrospective study, we did not have any information about water consumption patterns. Thus, our method assumes uniform water consumption rates across individuals and over time, and that women who resided in an area served by a CWS drank tap water (not filtered by reverse osmosis) from that system.

The number of samples and number of years of sample collection varied greatly by system. Surface water systems are generally required to collect and report arsenic levels

annually, while groundwater systems are required to report arsenic levels every three years (or more frequently if arsenic levels are above the EPA MCL). While most systems provided water service throughout the study period some CWSs were created in later years of the study period to provide service to newly created subdivisions, while others were not required to report arsenic levels due to a drop in the population served (common in mobile home parks). The use of BD values was also problematic, as they varied between and within years for different systems. These factors lead to exposure errors that cannot be quantified. Our sensitivity analyses, however, showed very little change in results using more stringent assumptions.

An additional limitation is that arsenic levels from all sources within a system were averaged to determine an annual arsenic level. Factoring in the timing and quantity of water from each source would provide a more accurate arsenic estimate. Review of individual water system records beyond that available in the SDWIS database was beyond the scope of this study.

We also did not know the length of time that women resided in the CWS providing service at the time of delivery. Residential mobility during pregnancy, reported in other studies to range from 20 to 30%, is an additional unknown (33-35). Most moves have been found to be in same general area. While a study of exposure to air contaminants would likely not be impacted by a move of a few miles, a move as little as across the street could result in a change of water system.

Errors in the exact boundaries of the CWS service areas, and in the geocoded locations of the maternal residence, would also affect the results. The large sample size, and efforts to validate CWS boundaries and residential locations, likely minimized any systematic errors that would result from these inaccuracies.

There is some limitation in generalizability due to the Utah population being predominantly White, with over half of the Utah population members of The Church of Jesus Christ of Latter Day Saints who follow religious proscriptions against alcohol and tobacco use, particularly in areas outside of Salt Lake County. Although smoking and alcohol use were lower,

and racial distribution differed (31, 33), in Utah compared with the US, the statistical significance of these risk factors was comparable to results from other studies.

Women who gave birth to more than one child during the 17-year study period were included in this study for each pregnancy. While some women lived in one CWS for all pregnancies, other women moved one or more times and may, or may not, have been exposed to differing levels of arsenic during subsequent pregnancies due to these moves. As risk may increase with chronic arsenic exposure, additional studies are recommended that assess residential mobility in terms of CWS exposure levels.

This study included all eligible births over a 17-year period, and used an SGA scale derived from Utah births. CWS service areas were carefully researched, and the assignment of maternal address to CWS was based on geocoding of actual street address. We thus expect there to be little error in linking arsenic levels to individuals. Further, most of the major known risk factors were included in the analysis. This adds credibility to the small but statistically significant associations with arsenic levels.

This study assessed exposure to arsenic levels common in populations where drinking water is supplied by a CWS. Women who lived outside of areas served by a CWS were not included in the analysis. In many areas of Utah, groundwater arsenic levels are among the highest in the US, with some even approaching those seen in heavily arsenic-impacted areas such as Bangladesh [4]. Additional studies are recommended in these areas to better elucidate the relationship of SGA at high arsenic levels, and to provide a basis for actions to reduce risk among populations using such wells.

References

(1) Frost FJ, Muller T, Petersen HV, et al. Identifying US populations for the study of health effects related to drinking water arsenic. J *Expo Anal Environ Epidemiol*. 2003;13(3):231-239.

(2) Lewis DR, Southwick JW, Scanlan LP, et al. The feasibility of epidemiologic studies of waterborne arsenic: a mortality study in Millard County, Utah. *J Envir Health*. 1998;60(9):14.

(3) Welch AH, Lico MS, Hughes JL. Arsenic in ground water of the western United States. *Ground Water*. 1988;26(3):333-347.

(4) Utah Department of Health, Panichello JD. Health Consultation: Arsenic Exposure in Culinary Drinking Water, Millard County, Utah. Agency for Toxic Substances and Disease Registry. 2009. (http://www.atsdr.cdc.gov/hac/pha/ArsenicExposureinMillardCountyUT/ArsenicExposureinUtahHC09-30-2009.pdf) (Accessed February 8, 2011).

(5) Lewis D, Southwick JW, Ouellet-Hellstrom R, et al. Drinking water arsenic in Utah: a cohort mortality study. *Environ Health Perspect*. 1999;107(5):359-365

(6) Agency for Toxic Substances and Diseases Registry. *Toxicological Profile for Arsenic*. Atlanta, GA: Agency for Toxic Substances and Diseases Registry; 2007.

(7) Bencko V. Carcinogenic, teratogenic, and mutagenic effects of arsenic. *Environ Health Perspect*. 1977;19:179-182.

(8) Klaasen CD. *Casarett & Doull's Toxicology: The Basic Science of Poisons. Fifth ed.* McGraw-Hill; 1996.

(9) Centeno JA, Mullick FG, Martinez L, et al. Pathology related to chronic arsenic exposure. *Environ Health Perspect*. 2002;110(Suppl 5):883-886.

(10) International Agency for Research on Cancer. Some drinking-water disinfectants and contaminants including arsenic. *IARC Monogr Eval Carcinog Risks Hum*. 2004;84:1-477.

(11) Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA*. 2008;300(7):814-822.

(12) Yang CY, Chang CC, Tsai SS, et al. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environ Res*. 2003;91(1):29-34.

(13) Hopenhayn C, Ferreccio C, Browning SR, et al. Arsenic exposure from drinking water and birth weight. *Epidemiology*. 2003;14(5):593-602.

(14) Huyck KL, Kile ML, Mahiuddin G, et al. Maternal arsenic exposure associated with low birth weight in Bangladesh. *J Occup Environ Med*. 2007;49(10):1097-1104.

(15) Rahman A, Vahter M, Smith AH, et al. Arsenic exposure during pregnancy and size at birth: a prospective cohort study in Bangladesh. *Am J Epidemiol*. 2008;169(3):304-312.

(16) Kwok RK, Kaufmann RB, Jakariya M. Arsenic in drinking water and reproductive health outcomes: a study of participants in the Bangladesh Integrated Nutrition Programme. *J Health Popul Nutr*. 2006;24(2):190-205.

(17) Myers SL, Lobdell DT, Liu Z, et al. Maternal drinking water arsenic exposure and perinatal outcomes in Inner Mongolia, China. *J Epidemiol Community Health*. 2010;64:325-329.

(18) California Environmental Protection Agency. Evidence on developmental and reproductive toxicity of inorganic arsenic. (http://www.oehha.ca.gov/Prop65/AS-HID.pdf) (Accessed October 15, 2008).

(19) Engel RR, Smith AH. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. *Arch Environ Health*. 1994; 49(5):418-427.

(20) Tseng CH, Chong CK, Chen CJ, et al. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis*. 1996;120(1-2):125-133.

(21) Chiou HY, Huang WI, Su CL, et al. Dose-response relationship between prevalence of cerebrovascular disease and ingested inorganic arsenic. *Stroke*. 1997;28(9):1717-1723.

(22) Wang CH, Jeng JS, Yip PK, et al. Biological gradient between long-term arsenic exposure and carotid atherosclerosis. *Circulation*. 2002;105(15):1804-1809.

(23) Concha G, Vogler G, Lezcano D, et al. Exposure to inorganic arsenic metabolites during early human development. *Toxicol Sci*. 1998;44(2):185-190.

(24) Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. *J Nutr*. 2003;133(suppl):1592S-1596S.

(25) US Environmental Protection Agency. Public Drinking Water Systems: Facts and Figures. (http://www.epa.gov/ogwdw/pws/factoids.html) (Accessed October 12, 2008).

(26) Utah Automated Geographic Reference Center. Utah SGID: Vector GIS Data Layers, By Category. Utah GIS Portal. (http://agrc.its.state.ut.us/) (Accessed September 10, 2008).

(27) Julian CG, Galan HL, Wilson MJ, et al. Lower uterine artery blood flow and higher endothelin relative to nitric oxide metabolite levels are associated with reductions in birth weight at high altitude. *Am J Physiol Regul Integr Comp Physiol*. 2008;295:906-915.

(28) Keyes LE, Armaza JF, Niermeyer S, et al. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. *Pediatr Res*. 2003;54:20-25.

(29) Jensen GM, Moore LG. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *Am J Public Health*. 1997;87:1003-1007.

(30) Utah Automated Geographic Reference Center. 10, 30, & 90 Meter Elevation Models (DEM). (http://gis.utah.gov/elevation-terrain-data/10-30-90-meter-elevation-models-dem-2) (Accessed October 12, 2010).

(31) US Census Bureau, American FactFinder. (http://factfinder.census.gov) (Accessed November 10, 2010).

(32) US Department of Agriculture, Economic Research Service. Rural-Urban Commuting Area Codes. (http://www.ers.usda.gov/ data/RuralUrbanCommutingAreaCodes/) (Accessed September 18, 2010).

(33) Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2000. *Morbidity and Mortality Weekly Report*. 2002;51(29):642-645.

(34) Canfield MA, Ramadhani TA, Langlois PH, et al. Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *J Expo Sci Environ Epidemiol*. 2006;16(6):538-543.

(35) Fell DB, Dodds L, King WD. Residential mobility during pregnancy. *Paediatr Perinat Epidemiol*. 2004;18(6):408-414.

(36) Khoury MJ, Stewart W, Weinstein A, et al. Residential mobility during pregnancy: implications for environmental teratogenesis. *J Clin Epidemiol*. 1988;41(1):15-20.

CHAPTER 3

ARSENIC IN COMMUNITY DRINKING WATER SYSTEMS AND PREGNANCY-RELATED HYPERTENSION

Abstract

Chronic exposure to high levels of arsenic has been associated with a number of cancers and diseases, including Blackfoot Disease, Type II diabetes, and, in some studies, hypertension. The purpose of this study was to investigate whether exposure to low to moderate levels of arsenic in drinking water is associated with pregnancy-related hypertension. Maternal addresses at time of delivery were geocoded for over 650,000 births to Utah residents during 1989–2006. Annual average arsenic levels were estimated for 476 Utah community water systems (CWSs) using monitoring data submitted to the Utah Department of Environmental Quality. Arsenic levels for each CWS were assigned to each birth based on conception year by linking geocoded addresses to georeferenced CWS service areas. The level of arsenic was not associated with increased risk of pregnancy-related hypertension in a model that adjusted for parity, body mass index, diabetes, weight gain, and other risk factors. Compared with tap water arsenic concentrations less than 2.5 micrograms per liter (μg/L), the adjusted odds ratio (aOR) for those with 2.5–5 μg/L was 0.97, 95% confidence interval: 0.93, 1.00; for those exposed to 5–10 μg/L, aOR 0.98, 95% confidence interval: 0.94, 1.02; and for those exposed to levels at or above 10 μg/L, aOR 0.99, 95% confidence interval: 0.93, 1.05.

Introduction

Arsenic is a naturally occurring element, widely distributed in the Earth's crust (1). Arsenic is released to the environment through wind-blown dust, erosion of rock, volcanic

eruptions, mining processes, pesticide application, coal and wood combustion, and waste incineration. Arsenic enters drinking water sources primarily through erosion, runoff, and leaching (1, 2). For most people, diet is the largest source of arsenic exposure, with additional exposure through drinking water, air, and incidental ingestion of contaminated soil (1). Exposure to arsenic in drinking water, however, is of primary concern since arsenic in drinking water is in the more toxic inorganic form, while arsenic in food sources is primarily the less toxic organic form of arsenic (3).

Groundwater arsenic levels vary widely across the United States (US), with higher levels in certain areas of many western states (4). In Utah, arsenic levels in drinking water range from below the limit of detection (BD) to over 400 micrograms per liter (µg/L) in some private wells (5, 6). Arsenic in Utah groundwater is primarily due to erosion of volcanic rock and to runoff and leaching in former mining and smelting areas (4, 6). The maximum contaminant level (MCL) for arsenic in community drinking water, as of January 2006, is 10 µg/L; the previous MCL was 50 µg/L (1).

Several adverse health outcomes have been linked to chronic exposure to arsenic, including cancers of the bladder, skin, lung, kidney, and liver, cardiovascular disease, and Blackfoot disease (1, 7-10). Studies in Taiwan, Bangladesh, and China found that hypertension was increased in populations exposed to arsenic levels as low as 21-50 µg/L in drinking water (11-14). Researchers in Bulgaria found elevated prevalence of preeclampsia (8.0 vs. 2.5 per 1,000 births) in women exposed to arsenic and other metals in air near a copper smelter (15-17). Placental arsenic content was also three times higher compared with those in the non-smelter area (16).

Pregnancy-related hypertension (PRH) includes preeclampsia and eclampsia. Preeclampsia, which occurs in 5% to 8% of pregnancies, is characterized by hypertension associated with proteinuria (18, 19). Eclampsia is the occurrence of seizures in women with signs and symptoms of preeclampsia. PRH generally occurs after 20 weeks gestation, and is implicated in preterm birth, perinatal morbidity and mortality, abruptio placenta, and intrauterine growth restriction (19, 20).

Inorganic arsenic readily crosses the placental barrier (1, 21), and several mechanisms by which arsenic may impact PRH have been suggested (22). Vascular endothelial cells are suspected to be primary targets of arsenic toxicity (23). Damage to the endothelium can result in edema and hemorrhage in various tissues and may increase the risk of preeclampsia (24). Arsenic has also been linked with inhibition of angiogenesis, defective placental vasculogenesis, and placental dysmorphogenesis, which may result in placental insufficiency (25). Arsenic has been shown to induce oxidative stress in the placenta (26, 27) and has been found to be elevated in placentas of women who live near smelters (15, 17). In preeclampsia, there is a partial failure in the placentation process, with reduced invasion of the spiral arteries by trophoblast (18) which may be due in part to increased oxidative stress (28).

The purpose of this study was to investigate whether there is an association between PRH and exposure to low to moderately elevated levels of arsenic in drinking water in a large, well-characterized cohort.

Methods

Study Design and Study Population

This is a retrospective cohort study of PRH in Utah residents, ages 18 or older, who had a live birth or stillbirth between January 1, 1989, and December 31, 2006, in Utah, and whose residence at the time was delivery was within the boundaries of a Community Water System (CWS). A CWS, as defined by the US Environmental Protection Agency (EPA), provides water to at least 15 residential service connections or at least 25 people year-round (29). The Safe Drinking Water Act requires that CWSs regularly monitor water quality, including arsenic levels. Maternal demographic data are presented in Table 3.1.

Upon approval of the study protocol by the Institutional Review Boards of the Utah Department of Health (UDOH) (Project #226) and the University of Utah (Project #00023217), the UDOH Office of Vital Records and Statistics provided birth and fetal death certificate data. For this study, PRH was based on the fields ‘Pregnancy-Associated Hypertension’ and/or ‘Eclampsia’ on birth certificates, and ‘Gestational Hypertension (PIH, preeclampsia,

Table 3.1 Maternal Demographics, PRH Study, Utah, 1989-2006

	Total#	%	#PRH	%PRH
Age				
18-19	41,480	6.1%	2,276	5.5%
20-24	216,131	32.0%	12,102	5.6%
25-29	222,646	32.9%	10,951	4.9%
30-34	132,951	19.7%	6,183	4.7%
>34	62,609	9.3%	3,641	5.8%
Race				
Black	4,652	0.7%	219	4.7%
Native American	7,499	1.1%	537	7.2%
White	639,057	95.1%	33,422	5.2%
Other races	20,676	3.1%	782	3.8%
Hispanic				
Yes	72,416	10.7%	3,329	4.6%
No	601,557	89.3%	31,737	5.3%
Education				
<12 years	80,237	12.0%	3,566	4.4%
12 years	218,551	32.8%	11,913	5.5%
>12 years	368,454	55.2%	19,232	5.2%
First pregnancy				
Yes	195,345	29.1%	15,002	7.7%
No	476,198	70.9%	19,980	4.2%
Marital status				
Married	576,848	85.4%	29,733	5.2%
Unmarried	98,947	14.6%	5,422	5.5%
Multiple pregnancy				
Yes	18,041	2.7%	2,081	11.5%
No	657,702	97.3%	33,071	5.0%
Pre-pregnancy BMI				
Lowest	43,692	7.1%	1,090	2.5%
Normal	374,801	60.7%	14,233	3.8%
Overweight	119,783	19.4%	8,352	7.0%
Obese	79,178	12.8%	8,736	11.0%
Smoking during pregnancy				
Yes	53,500	7.9%	2,204	4.1%
No	622,208	92.1%	32,944	5.3%
Alcohol during pregnancy				
Yes	9,109	1.4%	424	4.7%
No	662,355	98.6%	34,488	5.2%
Elevation at maternal residence				
<3,000 ft	3,994	0.6%	208	5.2%
3,000-4,000 ft	5,445	0.8%	295	5.4%
4,000-5,000 ft	592,930	87.8%	30,228	5.1%
5,000-6,000 ft	61,965	9.2%	3,682	5.9%
>6,000 ft	11,378	1.7%	739	6.5%
Rural/Urban Commuting Area				
Metropolitan	558,724	82.7%	28,854	5.2%
Metropolitan adjacent	45,463	6.7%	2,357	5.2%
Small town	42,632	6.3%	2,338	5.5%
Rural	29,007	4.3%	1,606	5.5%

eclampsia)' on fetal death certificates. We reviewed text fields on birth and fetal death records to identify and include cases of preeclampsia, eclampsia, or toxemia that had not been indicated as such in check box fields. Chronic hypertension was indicated in a separate field in the vital records and was not included in the definition of PRH for this study, as the focus of this study was on hypertension that began during pregnancy, and that included other diagnostic criteria such as proteinuria, edema, and/or seizures.

Non-resident births in Utah and births to Utah residents outside of Utah were excluded from the study, as were births that occurred in 1990 because addresses were not available on the electronic birth files for that year. Other exclusions included births a) with no address reported on the birth or fetal death certificate; b) with an address outside of a CWS service area; and c) where the address was within a CWS on tribal lands and water quality information was not available. Of the 725,014 Utah live births to women age 18 or older in 1989-2006, 52,916 (7.3%) were excluded from the study; 211 (5.4%) of the 3,943 stillbirths were also excluded. This left a final sample size of 675,830 (Figure 3.1).

Exposure Assignment

The UDOH provided geocoded coordinates for many of the maternal addresses, which were then reviewed to identify and correct errors. We then manually geocoded, where possible, the remaining addresses using ArcGIS 9.3 (ESRI, Redlands, CA). Addresses that included only a city and zip code, but the vital records identified that the woman lived within city limits were 1) geocoded to the center of the city, or 2) were geocoded to a zip code delivery centroid if more than one CWS provided service. Over 97% of the maternal addresses in each county were geocoded with sufficient precision to determine their CWS, or that they were outside of the boundaries of a CWS.

The Utah Department of Natural Resources (UDNR) provided a spatial database of most of the CWS boundaries statewide that had been created by the UDNR to provide the public with a general idea of CWS service areas. We reviewed each CWS boundary and revised boundaries, where indicated, based on water system maps (provided by several CWSs, county assessor

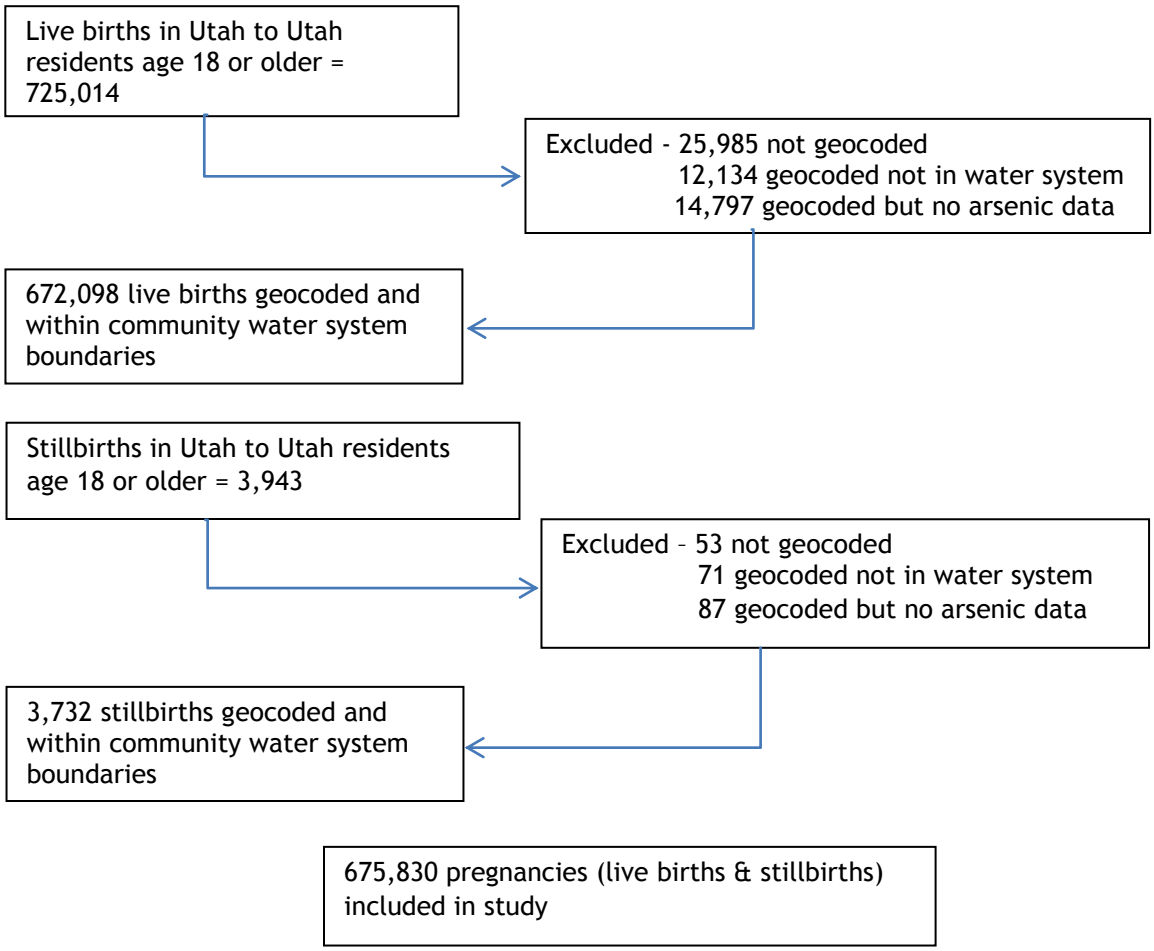

Figure 3.1 Pregnancy-Related Hypertension - Exclusion and Inclusion Criteria for Live Births and Stillbirths in Utah, 1989-2006

maps, and subdivision plat maps); legal descriptions of boundaries; Utah Department of Environmental Quality (UDEQ) electronic records of maps, mergers, boundary revisions, changes in ownership or system names,; and tax area boundaries (including municipalities, subdivisions, and several water systems) provided by the Utah Automated Geographic Reference Center (30). In reviewing the records of one CWS, we found that the CWS had seven regions that had differing water sources; a few of these areas had arsenic levels at 10-15 μg/L, while in other areas the arsenic levels were BD. As a result, we created seven different maps for the one CWS to more accurately assign arsenic exposures.

Through these various mapping sources, we were able to add 58 CWSs to the UDNR spatial database, and to refine the boundaries of over two-thirds of the CWS boundaries from the various sources. There were 13 systems (now closed) that were not mapped due to being unable to find any information on their boundaries. Twelve systems that were listed in the Safe Drinking Water Information System (SDWIS), but that only sold water to other systems, were also not mapped.

When map revisions were complete, geocoded residential address were then linked spatially to a CWS service area. Geocoded addresses that were outside of the boundaries of a CWS were then excluded from the study. Residences were also linked to geographic data layers that provided the elevation at the residence (31), the census block group (to assign median income and median housing values in 1990 and 2000) (32), and the Rural-Urban Commuting Area Codes for 1900 and 2000 (33). Residences of mothers who gave birth before 1995 were assigned the values for 1990, and those who gave birth in 1995-2006 were assigned values for 2000.

The annual averaged arsenic value for the CWS providing drinking water to the residence during the first trimester of pregnancy (based on gestational age reported in vital records) was then linked to each woman.

The arsenic concentration assigned to each woman was based on sample data in SDWIS reported by the CWS to the UDEQ during 1988 through 2007. While surface water systems are generally required to report arsenic levels every year, groundwater systems are only required

to report arsenic levels once every three years, unless arsenic levels from a prior year exceeded the MCL. In years where no sample result was reported or required, we used linear interpolation or extrapolation to assign the annual arsenic exposure estimate; for example, sample results reported in 1988 and 1991 were used to assign arsenic levels for 1989.

Arsenic concentrations for each source were averaged for the year they were reported, and we then averaged the values from all sources for that year to assign the arsenic concentration for each CWS. Most of the 470 CWSs were operational throughout the study period, but many of the CWSs began operation in later years to provide service to a new subdivision, or became classified as a CWS due to an increase in the population of the service area (common in systems serving mobile home parks). Many of the CWSs merged with other CWSs or began purchasing some or all of their water from other CWSs during the study period. Many of the CWSs blend water from various sources that at times differed in arsenic value. We carefully reviewed the sample data and water sources before assigning annual arsenic exposure estimates for CWS. We did not have information on the proportion of water from each source, nor did we know which sources were used only seasonally. Arsenic values reported for wells identified as “inactive” were not included in the estimate during years the wells were inactive.

Most samples reported as BD were assigned a value of half of the reported detection level. If the detection level was listed as zero, the value assigned was the higher value of 0.5 or half of the detection level listed for other samples for that system during that year. Where detection limits were listed as 50 µg/L, we reviewed the other sample values for that source during the time period and, where the high detection limit seemed unreasonable, a more realistic value was assigned based on the other sample data from that system. Differing BD values within and between systems increased the risk of potential error in the arsenic estimates. To reduce the magnitude of error, we coded each sample value to identify samples that included BD values so that the data could later be modeled including and excluding samples that were BD.

Analytical approach

The unit of analysis for this study is the individual mother. Bivariate analyses and multivariate logistic regression were used to assess the relationships between levels of arsenic in drinking water (and other covariates) with PRH. The measure of effect was the relative risk for PRH, adjusted for potential confounders and known risk factors. Statistical Analysis Systems software, version 9 (SAS, Cary NC) and Stata version 10 (Stata Corp., College Station, TX) were used for data reduction and statistical analyses.

After examining distributions of PRH and the covariates and potential collinear relationships, we then assessed bivariate relationships. Covariates were identified as potential confounders if they were associated with both arsenic exposure and PRH at a significance level of p-value < 0.2 in bivariate analyses. Known risk factors for PRH included in the initial main effects models included maternal age, maternal weight gain, body mass index (BMI), smoking, alcohol use, multiple pregnancy, elevation, maternal race/ethnicity, chronic hypertension, parity, diabetes, renal disease, abruptio placenta, placenta previa, and socioeconomic status. Proxy measures for socioeconomic status were years of education, and the median income and median housing values for the mother's census block group (32).

Elevation was categorized into 1,000 ft intervals ranging from <3,000 to >6,000. Arsenic concentration was assessed as a continuous variable and as a categorical variable. Sensitivity analyses were conducted to assess the effects of our assumptions in estimating annual average arsenic concentrations on the resulting associations with PRH. Finally, interaction terms were tested for all significant covariates that had the potential for effect modification.

Stepwise procedures were followed by diagnostic tests such as likelihood ratio tests, to assess significance and goodness-of-fit after the addition of each covariate. The statistical significance of the estimated parameters was assessed using two-sided tests with an alpha of 0.05.

Results

Compared with those exposed to arsenic levels less than 2.5 µg/L, there was no increase in PRH with increasing levels of arsenic exposure; the aORs for the higher exposure categories ranged from 0.97 to 0.99. Only 150 of the maternal residences (0.02% of the study population) were in CWS service areas that had estimated arsenic levels greater than 40 µg/L; the highest exposure level was 126.1 µg/L. The covariates included in the final model are shown in Table 3.2. Because arsenic levels were interpolated for years when sampling was not required and/or reported to UDEQ, we reanalyzed the data excluding interpolated values, and then excluding all BD values. In each of the follow-up analyses, increased arsenic levels were not significantly associated with increased rates of PRH, and the aORs were essentially the same.

A majority of the residences (74%) were in CWSs with arsenic levels less than 2.5 µg/L, were located in urban areas (83%), and were at less than 5,000 ft elevation. Over 55% of the population had more than 12 years education, and over 38% of the mothers were age 18-24.

The frequency of PRH was significantly increased at elevations greater than 6,000 feet (aOR 1.30, CI 1.10, 1.53), controlling for the covariates. PRH was increased at elevations between 5,000 to 6,000 feet, but the increase was not statistically significant.

Risk of PRH was significantly higher for women with higher BMI, with a threefold increase in women who were obese (aOR 3.11, CI 3.02, 3.20). Risks were also increased in women with diabetes (Type I or Type II, and gestational), in multiple pregnancies, in first pregnancies, and in women with comorbidities. PRH risk was increased in Native American women, and was decreased in Hispanic women.

The mean arsenic levels for the entire study period, sources (surface or groundwater), and location (metropolitan or nonmetropolitan) for the 476 CWSs are shown in Table 3.3. During the study period, over 86% of the CWSs had an overall average arsenic concentration that was less than 5 µg/L; only 6% of the CWSs had an average arsenic concentration over 10 µg/L.

Table 3.2 Covariates for PRH Study Included in Final Model, Utah, 1989-2006

	Total #	%	#PRH	%PRH	aOR	95% CI
Arsenic in Drinking Water						
<2.5 µg/L (ref)	499,207	73.9%	26,121	5.2%		
2.5-5.0 µg/L	95,238	14.1%	4,800	5.0%	0.97	(0.93, 1.00)
5.1-9.9 µg/L	56,444	8.4%	2,911	5.2%	0.98	(0.94, 1.02)
>9.9 µg/L	24,941	3.7%	1,323	5.3%	0.99	(0.93, 1.05)
Elevation at maternal residence						
<3,000 ft (ref)	3,994	0.6%	208	5.2%		
3,000-4,000 ft	5,445	0.8%	295	5.4%	0.95	(0.79, 1.15)
4,000-5,000 ft	592,930	87.8%	30,228	5.1%	0.89	(0.77, 1.03)
5,000-6,000 ft	61,965	9.2%	3,682	5.9%	1.09	(0.94, 1.27)
>6,000 ft	11,378	1.7%	739	6.5%	1.30	(1.10, 1.53)
Maternal age						
18-19	41,480	6.1%	2,276	5.5%	0.93	(0.89, 0.98)
20-24	216,131	32.0%	12,102	5.6%	1.03	(1.00, 1.06)
25-29 (ref)	222,646	32.9%	10,951	4.9%		
30-34	132,951	19.7%	6,183	4.7%	1.00	(0.96, 1.03)
>34	62,609	9.3%	3,641	5.8%	1.21	(1.16, 1.26)
Maternal Race						
Black	4,652	0.7%	219	4.7%	0.82	(0.71, 0.96)
Native American	7,499	1.1%	537	7.2%	1.10	(1.00, 1.21)
White (ref)	639,057	95.1%	33,422	5.2%		
Other races	20,676	3.1%	782	3.8%	0.66	(0.61, 0.71)
Hispanic						
Yes	72,416	10.7%	3,329	4.6%	0.82	(0.71, 0.96)
No (ref)	601,557	89.3%	31,737	5.3%		
Pre-pregnancy BMI						
Lowest	43,692	7.1%	1,090	2.5%	0.72	(0.68, 0.77)
Normal	374,801	60.7%	14,233	3.8%		
Overweight	119,783	19.4%	8,352	7.0%	1.74	(1.69, 1.79)
Obese	79,178	12.8%	8,736	11.0%	3.11	(3.02, 3.20)
Multiple pregnancy						
Yes	18,041	2.7%	2,081	11.5%	2.44	(2.32, 2.57)
No (ref)	657,702	97.3%	33,071	5.0%		
Type I or Type II diabetes						
Yes	2,056	0.3%	357	17.4%	2.74	(2.42, 3.10)
No (ref)	673,774	99.7%	34,798	5.2%		
Gestational diabetes						
Yes	10,202	1.5%	1,228	12.0%	1.94	(1.82, 2.07)
No (ref)	665,628	98.5%	33,927	5.1%		
Smoking during pregnancy						
Yes	53,500	7.9%	2,204	4.1%	0.80	(0.76, 0.84)
No (ref)	622,208	92.1%	32,944	5.3%		
Abruptio placenta						
Yes	7,984	1.2%	581	7.3%	1.57	(1.43, 1.72)
No (ref)	667,846	98.8%	34,574	5.2%		
Weight gain for BMI						
Recommended	266,235	39.4%	9,977	3.8%		
Low gain	159,758	23.6%	5,929	3.7%	0.89	(0.86, 0.92)
High gain	249,837	37.0%	19,249	7.7%	1.70	(1.65, 1.74)
Anemia (maternal)						
Yes	17,914	2.7%	1,192	6.7%	1.32	(1.24, 1.41)
No (ref)	657,916	97.3%	33,963	5.2%		

Table 3.2 continued

	Total #	%	#PRH	%PRH	aOR	95% CI
Renal disease (maternal)						
Yes	9,037	1.3%	885	9.8%	1.84	(1.71, 1.98)
No (ref)	666,793	98.7%	34,270	5.1%		
First pregnancy						
Yes	195,345	29.1%	15,002	7.7%	2.19	(2.14, 2.25)
No (ref)	476,198	70.9%	19,980	4.2%		
Cardiac disease (maternal)						
Yes	4,876	0.7%	404	8.3%	1.49	(1.33, 1.66)
No (ref)	670,954	99.3%	34,751	5.2%		
Respiratory disease (maternal)						
Yes	12,290	1.8%	1,103	9.0%	1.45	(1.35, 1.55)
No (ref)	663,540	98.2%	34,052	5.1%		

Table 3.3 Overall Mean Arsenic Concentrations (1989-2006) by Community Water System Attributes in Utah

Arsenic mean 1989-2006	CWS		Primarily Surface Water		Primarily Groundwater		Metropolitan		Non-Metropolitan	
µg/L	#	%	#	%	#	%	#	%	#	%
<2.5	290	61%	69	76%	221	57%	86	72%	204	57%
2.5-5	116	24%	16	18%	100	26%	21	18%	95	27%
5.1-9.9	43	9%	4	4%	39	10%	8	7%	35	10%
>9.9	27	6%	2	2%	25	6%	5	4%	22	6%
Total	476		91		385		120		356	

Over 80% of the CWSs relied primarily on groundwater; 7% of the groundwater systems had average arsenic levels of 10 µg/L or greater, compared with 2% of the systems supplied primarily by surface water. Only 25% of the water systems served metropolitan areas, and they had somewhat lower levels of arsenic.

Discussion

After adjusting for multiple potential confounders and known risk factors for PRH, we found no association between arsenic exposure and increased risk of PRH. The large sample size and substantial gradient of arsenic exposure levels provides good power to detect differences in PRH risk. As such, there is good evidence that arsenic exposures at these levels do not increase the risk of PRH.

These results are not consistent with the findings of the Tabacova studies in Bulgaria (16, 17) that found an association with preeclampsia and arsenic (and other metals), nor is it consistent with the studies conducted in China, Taiwan, and Bangladesh that found associations between arsenic in drinking water and hypertension (11-14). In the hypertension studies, however, the effects from arsenic exposure were seen at levels from 20-100 µg/L (11-14). Arsenic exposure levels were much lower in our study; the median level for the highest exposure group was 14.8 µg/L. The Tabacova studies in Bulgaria investigated arsenic exposures primarily through air near a copper smelter; the report also did not present additional information on other factors or exposures that could be associated with rate differences (15).

We also found a strong relationship between elevation greater than 6,000 feet and the risk of PRH, which is consistent with findings from Tibet, Bolivia, and Colorado (34-38). While PRH was increased, though not significantly, at elevations from 5,000 to 6,000 feet, there was no increase in PRH at elevations from 3,000 to 5,000 feet compared with lower elevation. Elevation exposure assignment was based on residential address, providing an increased level of accuracy in comparison to studies where elevation was based on county or census block location of the residence. Increased rates of PRH at high altitude are generally attributed to

chronic hypoxia; however, the mechanisms by which hypoxia acts to reduce fetal growth are not well understood (36-38).

Observed associations with known risk factors were as expected; PRH was significantly more common with obesity, excess weight gain, and nulliparity, and was less common with maternal smoking (39).

A major limitation of the study is lack of individual level data on water consumption, as this study relied on vital records data. Our method assumes uniform water consumption rates across individuals and over time, and that women who resided in an area served by a CWS drank tap water (not filtered by reverse osmosis) from that system.

CWSs differed in the number of samples and number of years of sample collection; however, reported arsenic levels within each CWS were generally consistent throughout the study period. The use of BD values was also problematic, as they varied between and within years for different systems, with reported detection limits ranging from 0 to 50 µg/L. These factors may lead to exposure errors which cannot be quantified. Our sensitivity analyses, however, showed very little change in results using more stringent assumptions. The overall general consistency in arsenic levels within systems also reduces the impact of these potential errors.

An additional limitation is that arsenic levels from all sources within a system were averaged to determine an annual arsenic level for each CWS. Factoring in the timing and quantity of water from each source would provide a much more accurate arsenic estimate. Review of individual water system records beyond that available in the SDWIS database, however, was beyond the scope of this study.

We also did not know in the length of time during the pregnancy (or earlier) that a woman lived at the residence within the CWS service area providing service at the time of delivery. Residential mobility during pregnancy has been reported in other studies to range from 20 to 30%. (40-44). Although most relocations have been found to be within the same general communities, a move across the street could result in a change of water system.

This study included women who were pregnant more than once during the study period. While some women lived in one residence (and one CWS) for all pregnancies, other women may have moved several times, and may or may not have been exposed to differing levels of arsenic during each pregnancy. As risk may increase with an increased number of years of chronic arsenic exposure, additional studies are recommended that assess residential mobility in terms of CWS exposure levels.

Many CWS boundaries change, sometimes greatly, over time to accommodate growing community needs for drinking water. Errors in the exact boundaries of the CWS service areas, and incorrectly geocoded maternal residences, would also affect the results. The large sample size, and efforts to validate CWS boundaries during the study time period and individual residential locations, likely minimized any systematic errors that would result from these inaccuracies.

There is some limitation in generalizability of these results due to differences in the racial distribution in Utah as compared to the US population, with 95.1% White in Utah (compared with 75.1% US), 0.7% Black (compared with 12.3% US), and 10.8% Hispanic (compared with 12.5% US) (32).

There were large potential differences in behavioral risk factors as well, as smoking and alcohol use are proscribed by the predominant religion in Utah. For example, less than 8% of the women in this study reported smoking, compared with the 23% national estimate in 2000 (45). In spite of these differences, the estimated effects of risk factors (other than arsenic) were comparable to results from other studies.

This study, however, included all eligible births over a 17-year period, CWS service areas were carefully researched, and the assignment of maternal address to CWS was based on geocoding of actual street address. We, thus, expect there to be little error in linking arsenic levels to individuals. In addition, most of the major known risk factors were included in the analysis. This adds credibility to the finding of no statistically significant association of PRH with arsenic at levels within the range of average annual sample values for the CWSs in this study.

This study only assessed exposure to arsenic levels common in populations where drinking water is supplied by a CWS. Women who lived outside of areas served by a CWS were not included in the analysis. In many areas of Utah, groundwater levels are among the highest in the US (4). Additional studies are recommended in these areas to investigate whether PRH is increased at high arsenic exposure levels, and to provide a basis for actions to reduce risk among women whose drinking water sources are private wells.

References

(1) Agency for Toxic Substances and Diseases Registry. *Toxicological Profile for Arsenic*. Atlanta, GA: Agency for Toxic Substances and Diseases Registry; 2007.

(2) Frost FJ, Muller T, Petersen HV, et al. Identifying US populations for the study of health effects related to drinking water arsenic. *J Expo Anal Environ Epidemiol*. 2003;13(3):231-239.

(3) Bencko V. Carcinogenic, teratogenic, and mutagenic effects of arsenic. *Environ Health Perspect*. 1977;19:179-182.

(4) Welch AH, Lico MS, Hughes JL. Arsenic in ground water of the western United States. *Ground Water*. 1988;26(3):333-347.

(5) Utah Department of Health, Panichello JD. Health Consultation: Arsenic Exposure in Culinary Drinking Water, Millard County, Utah. Agency for Toxic Substances and Disease Registry. 2009. (http://www.atsdr.cdc.gov/hac/pha/ ArsenicExposureinMillardCountyUT/ ArsenicExposureinUtahHC09-30-2009.pdf) (Accessed February 8, 2011).

(6) Lewis DR, Southwick JW, Scanlan LP, et al. The feasibility of epidemiologic studies of waterborne arsenic: a mortality study in Millard County, Utah. *J Envir Health*. 1998;60(9):14.

(7) Klaasen CD. *Casarett & Doull's Toxicology: The Basic Science of Poisons. Fifth ed*. New York, NY; McGraw-Hill; 1996.

(8) Centeno JA, Mullick FG, Martinez L, et al. Pathology related to chronic arsenic exposure. *Environ Health Perspect*. 2002;110(suppl):883-886.

(9) International Agency for Research on Cancer. Some drinking-water disinfectants and contaminants including arsenic. *IARC Monogr Eval Carcinog Risks Hum*. 2004;84:1-477.

(10) Navas-Acien A, Silbergeld EK, Pastor-Barriuso R, et al. Arsenic exposure and prevalence of type 2 diabetes in US adults. *JAMA*. 2008;300(7):814-822.

(11) Kwok RK, Mendola P, Liu ZY, et al. Drinking water arsenic exposure and blood pressure in healthy women of reproductive age in Inner Mongolia, China. *Toxicol Appl Pharmacol*. 2007;222:337-343.

(12) Chen CJ, Hsueh YM, Lai MS, et al. Increased prevalence of hypertension and long-term arsenic exposure. *Hypertension*. 1995;25:53-60.

(13) Rahman M, Tondel M, Ahmad SA, et al. Hypertension and arsenic exposure in Bangladesh. *Hypertension*. 1999;33:74-78.

(14) Kwok RK, Mendola P, Liu ZY. Changes in blood pressure during pregnancy associated with drinking water arsenic exposure in Inner Mongolia, China. *Ann Epidemiol*. 2004;14(8):621-624.

(15) Gomez-Caminero A, Howe P, Hughes M, et al. *Environmental Health Criteria 224, Arsenic and Arsenic Compounds, Second Edition*. United Nations Environment Programme, International Labour Organization, and World Health Organization , 2001. (http://www.who.int/ipcs/publications/ehc/224_As_Part_1.pdf) (Accessed February 20, 2011).

(16) Tabacova S, Little RE, Balabaeva L, et al. Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. *Reprod Toxicol*. 1994;8(3):217-224.

(17) Tabacova S, Balabaeva L. Environmental pollutants in relation to complications of pregnancy. *Environ Health Perspect*. 1993;101(suppl):27-31.

(18) Reynolds C, Mabie WC, Sibai BM. Hypertensive States of Pregnancy. In: *Current Obstetric & Gynecologic Diagnosis & Treatment*. *9th Edition*. DeCherney AH, Nathan L, eds. New York, NY; McGraw-Hill; 2003:338-353.

(19) Thadhani R, Solomon CG. Preeclampsia – a glimpse into the future? *N Engl J Med*. 2008;359(8):858-860.

(20) Cunningham F, Lindheimer M. Hypertension in pregnancy. *N Engl J Med*. 1992;326:927-932.

(21) Concha G, Vogler G, Lezcano D, et al. Exposure to inorganic arsenic metabolites during early human development. *Toxicol Sci*. 1998;44(2):185-190.

(22) California Environmental Protection Agency. Evidence on developmental and reproductive toxicity of inorganic arsenic. (http:// www.oehha.ca.gov/Prop65/AS-HID.pdf) (Accessed October 15, 2008).

(23) Engel RR, Smith AH. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. *Arch Environ Health*. 1994; 49(5):418-427.

(24) Prozialeck WC, Edwards JR, Nebert DW, et al. The vascular system as a target of metal toxicity. *Toxicol Sci*. 2008;103(2):207-218.

(25) He W, Greenwell RJ, Brooks DM, et al. Arsenic exposure in pregnant mice disrupts placental vasculogenesis and causes spontaneous abortion. *Toxicol Sci*. 2007;14:175.

(26) Jha AN, Noditi M, Nilsson R, et al. Genotoxic effects of sodium arsenite on human cells. *Mutat Res*. 1992;284:215-221.

(27) Vahter M. Health effects of early life exposure to arsenic. *Basic Clin Pharmacol Toxicol*. 2008;102:204-211.

(28) Myatt L, Cui X. Oxidative stress in the placenta. *Histochem Cell Biol*. 2004;122:369-382.

(29) US Environmental Protection Agency. Public Drinking Water Systems: Facts and Figures. (http://epa.gov/ogwdw/pws/factoids.html) (Accessed October 12, 2008).

(30) Utah Automated Geographic Reference Center. Utah SGID: Vector GIS Data Layers, By Category. Utah GIS Portal. (http://agrc.its.state.ut.us/) (Accessed September 10, 2008).

(31) Utah Automated Geographic Reference Center. 10, 30, & 90 Meter Elevation Models (DEM). (http://gis.utah.gov/elevation-terrain-data/10-30-90-meter-elevation-models-dem-2) (Accessed October 12, 2010).

(32) US Census Bureau, American FactFinder. (http://factfinder.census.gov) (Accessed November 10, 2010).

(33) US Department of Agriculture, Economic Research Service. Rural-Urban Commuting Area Codes. (http://www.ers.usda.gov/Data/ RuralUrbanCommutingAreaCodes/) (Accessed September 18, 2010).

(34) Keyes LE, Armaza JF, Niermeyer S, et al. Intrauterine growth restriction, preeclampsia, and intrauterine mortality at high altitude in Bolivia. *Pediatr Res*. 2003;54:20-25.

(35) Miller S, Tudor C, Nyima, et al. Maternal and neonatal outcomes o hospital vaginal deliveries in Tibet. *Int J Gyn Obstet*. 2007;98:217-221.

(36) Julian CG, Galan HL, Wilson MJ, et al. Lower uterine artery blood flow and higher endothelin relative to nitric oxide metabolite levels are associated with reductions in birth weight at high altitude. *Am J Physiol Regul Integr Comp Physiol*. 2008;295:906-915.

(37) Jensen GM, Moore LG. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? *Am J Public Health*. 1997;87:1003-1007.

(38) Zamudio S, Palmer SK, Dahms TE, et al. Blood volume expansion, preeclampsia, and infant birth at high altitude. *J Appl Physiol*. 1993;75(4):1566-1573.

(39) England L, Zhang J. Smoking and risk of preeclampsia: a systematic review. *Front Biosci*. 2007;12:2471-2483.

(40) Canfield MA, Ramadhani TA, Langlois PH, et al. Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *J Expo Sci Environ Epidemiol*. 2006;16(6):538-543.

(41) Fell DB, Dodds L, King WD. Residential mobility during pregnancy. *Paediatr Perinat Epidemiol*. 2004;18(6):408-414.

(42) Khoury MJ, Stewart W, Weinstein A, et al. Residential mobility during pregnancy: implications for environmental teratogenesis. *J Clin Epidemiol*. 1988;41(1):15-20.

(43) Lupo PJ, Symanski E, Chan W, et al. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. *Paediatr Perinat Epidemiol*. 2010;24(2):200-208.

(44) Chen L, Bell EM, Caton AR, et al. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. *Environmental Research*. 2010;110(2):162-168.

(45) Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2000. *Morbidity and Mortality Weekly Report*. 2002;51(29):642-645.

CHAPTER 4

ARSENIC IN COMMUNITY DRINKING WATER SYSTEMS AND STILLBIRTH

Abstract

Chronic exposure to high levels of arsenic in drinking water has been associated with a number of adverse reproductive outcomes, including stillbirth, spontaneous abortion, and lower birth weight. Most studies of exposure to arsenic have been in areas such as Bangladesh or Taiwan where arsenic levels in drinking water were extremely elevated. Very few studies have investigated health effects from exposure to levels of arsenic common in Community Water Systems (CWSs) in the United States. Maternal addresses at time of delivery were geocoded for over 650,000 births and stillbirths in Utah during 1989–2006. Annual average arsenic levels were estimated for 476 Utah CWSs using monitoring data submitted to the Utah Department of Environmental Quality. Annual arsenic levels for each CWS were assigned to each birth and stillbirth based on conception year by linking geocoded addresses to georeferenced service areas for each CWS. Multiple births and infants with birth defects were excluded from the study. The level of arsenic was not associated with incidence of stillbirth in a model that adjusted for maternal age, diabetes, birth weight, preterm birth, weight gain, and other risk factors. Compared with women whose tap water arsenic concentrations were less than 2.5 micrograms per liter (µg/L), the adjusted odds ratio (aOR) for those with 2.5–5 µg/L was 1.15, 95% confidence interval (CI): 1.00, 1.31; for those with 5–10 µg/L, aOR 0.77, (CI 0.65, 0.91; and for those at or above 10 µg/L, aOR 0.88, (CI 0.70, 1.10).

Introduction

Chronic exposure to high levels of arsenic in drinking water has long been linked to a number of cancers and diseases (1-5), particularly in areas such as Bangladesh and Taiwan where arsenic levels are extremely high. Evidence linking exposure to arsenic in drinking water with adverse birth outcomes has been less consistent. Stillbirth, for example, was found to be associated with increased arsenic exposure in drinking water in studies in Chile, Bangladesh, India, and Hungary (6-12), while studies in China, Bangladesh and Massachusetts found no association between stillbirth and arsenic exposure (13-16).

Arsenic is released into the environment through natural processes of erosion, leaching, and wind-blown soil (1, 17). Pesticide application, mining activities, waste incineration, and combustion of wood or coal are other major sources of arsenic releases to air, water, and soil. In Utah, weathering of volcanic rocks and erosion of slag and soil from past mining activities are the major sources of arsenic in groundwater (18, 19). Arsenic levels in groundwater arsenic levels vary greatly across the US, and across Utah as well; arsenic levels in drinking water in Utah range from below the limit of detection (BD) to over 400 micrograms per liter (μg/L) in some private wells (20, 21).

There is no universally accepted definition for stillbirth (22). In the US, stillbirth usually refers to a fetal death after 20 weeks gestation; pregnancy loss before 20 weeks is defined as a spontaneous abortion. In Utah, fetal death certificates are required for fetal deaths at 20 or more weeks of gestation (23). The incidence of stillbirth in Utah is approximately 4.9 per 1,000 live births.

Although many studies of the effects of arsenic have been conducted in vivo, and in vitro, the exact biologic mechanisms underlying the effects of arsenic are unknown (24). Inorganic arsenic readily crosses the placental barrier (1, 25). Vascular endothelial cells are suspected to be primary targets of arsenic toxicity (26). Mechanical and chemical injury of the vascular endothelium triggers a cascade of processes that individually and jointly can result in adverse outcomes. Arsenic exposure has also been found to cause defective placental vasculogenesis and placental dysmorphogenesis that may result in placental insufficiency and

subsequent spontaneous abortion (27). Arsenic has also been found to increase oxidative stress, which is seen in pregnancies complicated by preeclampsia and intrauterine growth restriction (28), which are both risk factors for stillbirth (29).

The purpose of this study was to investigate whether there is an association between stillbirth and exposure to low to moderately elevated levels of arsenic in drinking water.

Methods

Study Design and Study Population

This is a retrospective cohort study of stillbirth occurrence in Utah residents during January 1, 1989, to December 31, 2006. For this study "stillbirth" is defined as 1) pregnancy loss at 20 weeks gestation or later in Utah recorded on a fetal death certificate, and 2) pregnancy loss where a birth certificate was issued but the 1-minute and 5-minute Apgar scores were both zero.

Fetal death and birth certificate data were obtained from the Utah Department of Health (UDOH) Office of Vital Records and Statistics. Maternal addresses were provided electronically for births; maternal addresses for stillbirths were transcribed directly from fetal death certificates by the research team.

Utah residents ages 18 and older, and whose residential addresses as listed on birth or fetal death certificates were within the boundaries of a CWS, were included in the study. (See Table 4.1 for maternal demographic data.) A CWS is a water system that provides drinking water to at least 15 residential service connections or at least 25 people year-round, and as such, is regulated under the Safe Drinking Water Act and required to conduct regular monitoring of water quality (30).

Multiple births, infants with birth defects, and fetal deaths identified in vital records as being due to trauma, maternal death, infection, or breech delivery were excluded. Other exclusions included births and stillbirths: a) outside of Utah to Utah residents; b) with no address reported on the birth or fetal death certificate; c) where address information was inadequate to identify whether or not the maternal address was within the boundaries of a

Table 4.1 Maternal Demographics for Stillbirth Study, Utah, 1989-2006

	Total #	%	# Stillbirths	%
Age				
18-19	39,701	6.2%	144	0.36%
20-24	205,891	32.2%	645	0.31%
25-29	210, 879	33.0%	712	0.34%
30-34	125,045	19.5%	533	0.43%
>34	58,398	9.1%	415	0.71%
Race				
Black	4,306	0.7%	30	0.70%
Native American	7,128	1.1%	38	0.53%
White	605,032	93.7%	2,285	0.38%
Other races	19,712	3.1%	86	0.44%
Hispanic				
Yes	68,873	10.8%	335	0.49%
No	569,294	89.2%	2,124	0.37%
Education				
<12 years	75,733	12.0%	1,206	1.59%
12 years	207,307	32.8%	425	0.21%
>12 years	348,812	55.2%	683	0.20%
Marital status				
Married	546,080	85.3%	1,974	0.36%
Unmarried	93,822	14.7%	465	0.50%
Smoking during pregnancy				
Yes	50,743	7.9%	235	0.46%
No	589,101	92.1%	2,144	0.36%
Alcohol during pregnancy				
Yes	8,642	1.4%	36	0.42%
No	627,371	98.6%	1,893	0.30%
First pregnancy				
Yes	187,140	29.4%	752	0.40%
No	448,827	70.6%	1,588	0.35%
Type I or Type II diabetes				
Yes	1,843	0.3%	40	2.17%
No	638,081	99.7%	2,419	0.38%
Gestational diabetes				
Yes	9,470	1.5%	32	0.34%
No	630,454	98.5%	2,427	0.38%
Pre-pregnancy BMI				
Lowest	41,479	7.1%	132	0.32%
Normal	355,650	60.8%	1,177	0.33%
Overweight	113,285	19.4%	475	0.42%
Obese	74,396	12.7%	409	0.55%
Weight gain for BMI				
Recommended	254,858	39.8%	494	0.19%
Low gain	151,796	23.7%	1,589	1.05%
High gain	233,270	36.5%	376	0.16%
Rural/Urban Commuting Area				
Metropolitan	529,096	82.2%	2,021	0.38%
Metropolitan adjacent	43,003	7.7%	188	0.44%
Small town	40,293	6.1%	149	0.37%
Rural	27,528	4.1%	101	0.37%

CWS; d) that occurred in 1990 because addresses were not available on the electronic birth files for that year; and e) where the address was within a tribal CWS and water quality information was not available.

Of the 3,943 stillbirths, 725 stillbirths in Utah to women age 18 or older in 1989-2006, 1,484 (37.6%) were excluded from the study; 87,549 (12.1%) of the 725,014 live births were excluded. This left a final sample size of 639,924, including 637,465 live births and 2,459 fetal deaths, of which 119 were identified on the basis of the 1-minute and 5-minute Apgar scores (Figure 4.1).

Exposure Assignment

Water quality data from the Safe Drinking Water Information System (SDWIS), that included 27,500 arsenic sample results for years 1978-2007, was provided by the Utah Department of Environmental Quality (UDEQ) for all water systems. We used these data to estimate annual average arsenic concentrations for each CWS. When there was no sample result reported for a given year, we used linear interpolation or extrapolation to estimate arsenic values.

Some CWSs had consistent water sources for the entire time period, while others merged with other systems or began purchasing water from other CWSs, particularly in later years, to improve water quality or to consolidate regionally to provide more efficient service. CWSs commonly blend water from various sources that may have different arsenic levels. Where a CWS had two or more water sources, we first averaged the arsenic values reported that year for each source, and then averaged the arsenic values for all sources.

Water volumes from different sources are often not equal, and some sources are used only seasonally; however, data on water volume and number of days annually that each source was used were not available for this study. As a result, all sources within a CWS were assumed to have contributed equally.

Where a sample value was reported as BD, we generally assigned the sample a value of half of the detection level reported in SDWIS for that sample. In doing so, imprecision was

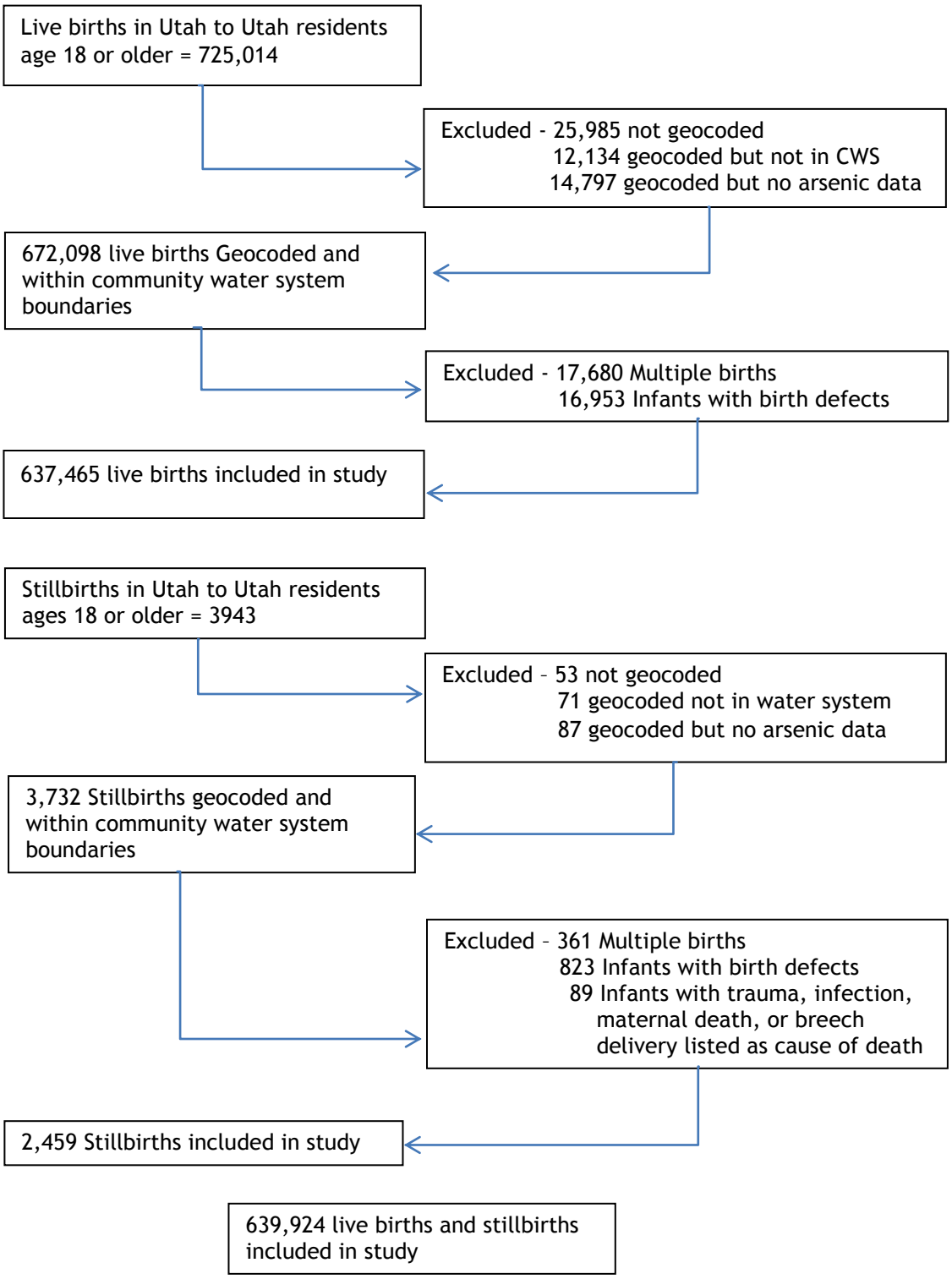

Figure 4.1 Stillbirth Study – Exclusion and Inclusion Criteria for Live Births and Fetal Deaths in Utah, 1989-2006

added to the estimate for that water source, particularly since the reported detection levels were not consistent between CWSs within a year, nor were they consistent over time due to changes in technology and the use of different laboratories. To address these inconsistencies, annual sample values for each CWS were coded to identify samples that included BD values, and sensitivity analyses were carried out.

Maternal addresses from the birth and fetal death certificates were geocoded using ArcGIS® 9.3 (ESRI, Redlands, CA). Only 1% of the maternal addresses for the stillbirths were not geocoded, and these were due to missing address data. Over 97% of the maternal addresses for the live births in each county were geocoded with sufficient precision to determine their CWS, or that they were outside of the boundaries of a CWS.

The Utah Department of Natural Resources (UDNR) provided a spatial database of CWS service area boundaries. Using publicly available information and records from the UDEQ and Utah Automated Geographic Reference Center, CWS boundaries were updated, and 53 CWSs were added to the database. The geocoded addresses were then linked to the CWS spatial database. Maternal addresses were also linked to census block group (for median income and median housing value information) (31) and to Rural-Urban Area Code boundaries (32).

Finally, each birth and stillbirth was linked to the annual estimated arsenic concentration for the CWS that provided service at the maternal residence during first trimester of the year in which pregnancy occurred (based on gestational age reported on in vital records).

Analytical Approach

The individual births and stillbirths are the units of analysis for this study. Bivariate analyses and multivariate logistic regression were used to assess the relationship between differing levels of arsenic in drinking water and stillbirth, and to assess the degree of correlation between covariates. Covariates were identified as potential confounders if they were associated with both arsenic exposure and stillbirth at a significance level of p-value < 0.2 in bivariate analyses. The odds ratio, adjusted for known risk factors and potential

confounders, was the measure of effect. Stata version 10 (College Station, TX) and Statistical Analysis Systems (SAS) software, version 9 (Cary NC), were used for data processing and statistical analyses.

Potential confounders and known risk factors for stillbirth in the initial main effects models included preterm birth, low birth weight, smoking, alcohol use, diabetes, maternal race/ethnicity, parity, chronic hypertension, pregnancy-related hypertension, renal disease, abruptio placenta, cord prolapse, placenta previa, anemia, and socioeconomic status. Median family income and median housing values (based on census block group) (31), and education were used as proxy measures for socioeconomic status.

Arsenic concentration was assessed as a continuous variable and as a categorical variable. Sensitivity analyses were conducted to assess the effects of our assumptions in estimating annual average concentrations on the resulting associations with stillbirth. Interaction terms were tested for all covariates that previous studies or etiology suggested had the potential for effect modification. Stepwise procedures, followed by likelihood ratio tests, were used to assess significance and goodness-of-fit after the addition of each covariate. Two-sided tests with an alpha of 0.05 were used to assess statistical significance.

The Institutional Review Boards from the University of Utah (Project #00023217) and from the UDOH (Project #226) approved the study protocol.

Results

Compared with arsenic levels less than 2.5 µg/L, there was no increase in stillbirth with increasing levels of arsenic exposure (Table 4.2). The aOR was less than 1 for arsenic levels > 5.0 µg/L, but there was no consistent trend. The continuous arsenic concentration measure was likewise nonsignificant with an odds ratio near one (aOR 0.99; 95% CI 0.97, 1.00). Arsenic levels were less than 2.5 µg/L for the majority of the residences (73.8%). The median exposure level in the highest arsenic category was 11.7 µg/L (mean 13.0 µg/L). Only 144 of the women (0.02% of the study population) lived in CWS service areas that had estimated arsenic levels greater than 40 µg/L; the highest exposure level was 126.1 µg/L.

Table 4.2 Covariates Included in Final Model for Stillbirth Study, Utah, 1989-2006

	Total #	%	#Stillbirths	%	aOR	95% CI
Arsenic in Drinking Water						
<2.5 µg/L (ref)	472,521	73.8%	1,821	0.39%		
2.5-5.0 µg/L	90,341	14.1%	342	0.38%	1.12	(0.96, 1.30)
5.1-9.9 µg/L	53,435	8.4%	200	0.37%	0.73	(0.60, 0.88)
>9.9 µg/L	23,627	3.7%	96	0.41%	0.82	(0.63, 1.07)
Maternal age						
18-19	39,701	6.2%	144	0.36%	0.34	(0.27, 0.42)
20-24	205,891	32.2%	645	0.31%	0.65	(0.57, 0.74)
25-29 (ref)	210,879	33.0%	712	0.34%		
30-34	125,045	19.5%	533	0.43%	1.16	(1.00, 1.34)
>34	58,398	9.1%	415	0.71%	1.58	(1.34, 1.85)
Education						
<12 years	75,733	12.0%	1,206	1.59%	7.46	(6.52, 8.55)
12 years (ref)	207,307	32.8%	425	0.21%		
>12 years	348,812	55.2%	683	0.20%	0.99	(0.85, 1.14)
Pre-pregnancy BMI						
Lowest	41,479	7.1%	132	0.32%	0.57	(0.46, 0.70)
Normal	355,650	60.8%	1,177	0.33%		
Overweight	113,285	19.4%	475	0.42%	1.29	(1.13, 1.47)
Obese	74,396	12.7%	409	0.55%	1.24	(1.07, 1.42)
Weight gain for BMI						
Recommended	254,858	39.8%	494	0.19%		
Low gain	151,796	23.7%	1,589	1.05%	2.00	(1.77, 2.27)
High gain	233,270	36.5%	376	0.16%	0.95	(0.82, 1.11)
Birth weight						
Low birth weight	26,414	4.1%	389	1.47%	5.49	(4.60, 6.56)
Very low birth weight	5,326	0.8%	1,215	22.81%	67.7	(56.2, 81.5)
Not low birth weight (ref)	607,694	95.0%	646	0.11%		
Preterm						
Yes	48,370	7.6%	1,742	3.60%	2.84	(2.40, 3.37)
No (ref)	591,554	92.4%	717	0.12%		
Anemia (maternal)						
Yes	16,488	2.6%	402	2.44%	6.78	(5.84, 7.88)
No (ref)	623,436	97.4%	2,057	0.33%		
Type I or Type II diabetes						
Yes	1,843	0.3%	40	2.17%	1.84	(1.15, 2.96)
No (ref)	638,081	99.7%	2,419	0.38%		
Abruptio placenta						
Yes	7,186	1.1%	314	4.37%	1.46	(1.23, 1.73)
No (ref)	632,738	98.9%	2,145	0.34%		
Cord prolapse						
Yes	1,571	0.3%	41	2.61%	2.32	(1.47, 3.66)
No (ref)	638,353	99.8%	2,418	0.38%		

As arsenic levels were interpolated for years when sampling was not required and/or was not reported to UDEQ, we repeated the analyses first excluding interpolated values, and then excluding all BD values. In each of the follow-up analyses, increased arsenic levels were not significantly associated with increased rates of stillbirth, and the aORs were essentially the same. See Table 4.2 for the covariates included in the final model.

Observed associations between known risk factors and stillbirth were statistically significant. Risk of stillbirth was highest in very low birth weight pregnancies (aOR 67.7, CI 56.2, 81.5); in women with less than 12 years education (aOR 7.46, CI 6.52, 8.55); and in women with anemia, (aOR 6.78, CI 5.84, 7.88). Risks for stillbirth were also increased in women over age 34, in preterm births, in women who gained less weight than recommended for their body mass index (BMI), in women with Type I or Type II diabetes (but not gestational diabetes), and in women with pregnancy complications.

In the bivariate analyses, stillbirth risk was increased in Black women (aOR 1.85, CI 1.29, 2.66); in Native American women (aOR 1.41, CI 1.03, 1.95); and in Hispanic women (aOR 1.31, CI 1.16, 1.47). Race and ethnicity, however, were highly correlated with low birth weight and education, leading to unstable estimates in the logistic regression; as such, they were not included in the final model.

Discussion

After adjusting for multiple potential confounders and known risk factors for stillbirth, we found no association between arsenic exposure and increased risk of stillbirth. Studies to date on whether stillbirth is associated with arsenic exposure in drinking water have had mixed results (6-16). Studies with positive findings were in areas with very high arsenic levels, with arsenic reference levels ranging from 50 to 200 µg/L of arsenic. Our study examined effects at much lower levels; the median level for the highest exposure group was 11.7 µg/L (mean 13.0 µg/L), and the reference level for arsenic was 2.5 µg/L.

While it is possible that exposures to these moderate levels may result in only modest excess risks that are difficult to detect, the large sample size, inclusion of all births and

stillbirths in Utah over a 17-year period, and completeness of address geocoding in this study provide evidence that any excess risk would be quite small. Exposure assignment, however, was limited by the lack of individual level data on water consumption. The exposure metric does not reflect the variability in exposure due to differences in the amount of home tap water consumed, exposure from drinking water at work or at other locations, or the effects of home treatment using reverse osmosis.

The number of samples and number of years of sample collection and reporting varied in the 476 CWSs; some systems reported arsenic sample results every year of the study time period, while some systems were only operational for one to three years of the time period. The BD values also varied by system and over time, which may lead to exposure errors; our sensitivity analyses, however, showed very little change in results. Averaging arsenic levels from all sources to determine an annual average arsenic level, without factoring in when each source was being used and how much it produced, also affected the precision and accuracy of the exposure estimates. Review of individual CWS records beyond that available in the SDWIS database, however, was beyond the scope of the study.

We also did not know whether the address recorded on vital records at the time of delivery was where the mother lived during the critical early months of the pregnancy. Residential mobility during pregnancy has been reported in other studies to range from 20 to 30% (33-37). While most moves have been found to be within the same general community, in some cases moving even a very short distance could result in being served by a different CWS that may have higher or lower arsenic levels. In addition, many of the women in the study had more than one pregnancy during the study time period, and may have lived in several different CWS services areas with varying levels of arsenic exposure during these pregnancies. A study by Ahmad in Bangladesh found that women exposed to high levels of arsenic in drinking water for greater than 15 years had a stillbirth rate of 77.5 per 1,000, while the rate in those exposed for less than 15 years was 43.5 per 1,000 (10). As risks may increase with length of time of exposure to higher levels of arsenic, additional studies are recommended to better identify timing of exposure to arsenic during and prior to each pregnancy.

There is some limitation in generalizability due to differences in the racial and religious breakdown of the Utah population. Utah is predominantly White (95.1% compared with 75.1% US), with only 0.7% Black (compared with 12.3% US) and 10.8% Hispanic (compared with 12.3% US) (31). Another major difference is that over half of the Utah population members of The Church of Jesus Christ of Latter Day Saints who follow religious proscriptions against tobacco and alcohol consumption. Less than 8% of the women in our study reported smoking, compared with the 23% national estimate for 2000 (38).

This study included all eligible births over a 17-year period. CWS service areas were carefully researched, and the assignment of maternal address to CWS was based on geocoding of actual street address. As a result, we expect there to be little error in linking arsenic levels to individuals. Further, most of the major known risk factors were included in the analysis. This adds credibility to the finding of no statistically significant association of stillbirths with arsenic levels in drinking water within the range of average annual sample value for the CWSs in this study.

This study assessed exposures to arsenic concentrations common in US populations that whose drinking water is supplied by a CWS. Women whose drinking water was supplied by private wells were not included in the analysis. In a few areas of Utah, groundwater arsenic levels are some of the highest in the US (20, 21). Additional studies are recommended in areas where private wells have high arsenic levels to better assess the relationship of stillbirth at high arsenic levels, and to provide a basis to determine whether additional actions are warranted to reduce risk among those using such wells.

References

(1) Agency for Toxic Substances and Diseases Registry. *Toxicological Profile for Arsenic*. Atlanta, GA: Agency for Toxic Substances and Diseases Registry; 2007.

(2) Klaasen CD. *Casarett & Doull's Toxicology: The Basic Science of Poisons. Fifth ed*. New York, NY:McGraw-Hill; 1996.

(3) Centeno JA, Mullick FG, Martinez L, et al. Pathology related to chronic arsenic exposure. *Environ Health Perspect*. 2002;110(suppl):883-886.

(4) International Agency for Research on Cancer. Some drinking-water disinfectants and contaminants including arsenic. *IARC Monogr Eval Carcinog Risks Hum*. 2004;84:1-477.

(5) Tseng CH, Chong CK, Chen CJ, et al. Dose-response relationship between peripheral vascular disease and ingested inorganic arsenic among residents in blackfoot disease endemic villages in Taiwan. *Atherosclerosis*. 1996;120(1):125-133.

(6) Hopenhayn-Rich C, Browning SR, Hertz-Picciotto I, et al. Chronic arsenic exposure and risk of infant mortality in two areas of Chile. *Environ Health Perspect*. 2000;108(7): 667-673.

(7) Milton AH, Smith W, Rahman B, et al. Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh. *Epidemiology*. 2005;16(1):82-86.

(8) Cherry N, Shaikh K, McDonald C, et al. Stillbirth in rural Bangladesh: arsenic exposure and other etiological factors: a report from Gonoshasthaya Kendra. *Bull World Health Organ*. 2008;86(3):172-177.

(9) Rahman A, Vahter M, Ekstrom EC, et al. Association of arsenic exposure during pregnancy with fetal loss and infant death: a cohort study in Bangladesh. *Am J Epidemiol*. 2007;165(12):1389-1396.

(10) Ahmad SA, Sayed MH, Barua S, et al. Arsenic in drinking water and pregnancy outcomes. *Environ Health Perspect*. 2001;109(6):629-631.

(11) von Ehrenstein OS, Guha Mazumder DN, Hira-Smith M, et al. Pregnancy outcomes, infant mortality, and arsenic in drinking water in West Bengal, India. *Am J Epidemiol*. 2006;163(7):662-669.

(12) Borzsonyi M, Bereczky A, Rudnai P, et al. Epidemiological studies on human subjects exposed to arsenic in drinking water in southeast Hungary. *Arch Toxicol*. 1992;66(1):77-78.

(13) Myers SL, Lobdell DT, Liu Z, et al. Maternal drinking water arsenic exposure and perinatal outcomes in Inner Mongolia, China. *J Epidemiol Community Health*. 2010;64:325-329.

(14) Kwok RK, Kaufmann RB, Jakariya M. Arsenic in drinking water and reproductive health outcomes: a study of participants in the Bangladesh Integrated Nutrition Programme. *J Health Popul Nutr*. 2006;24(2):190-205.

(15) Rahman A, Persson LA, Nermell B, et al. Arsenic exposure and risk of spontaneous abortion, stillbirth, and infant mortality. *Epidemiol*. 2010;21(6):797-804.

(16) Aschengrau A, Zierler S, Cohen A. Quality of community drinking water and the occurrence of spontaneous abortion. *Arch Environ Health*. 1989;44(5):283-290.

(17) Frost FJ, Muller T, Petersen HV, et al. Identifying US populations for the study of health effects related to drinking water arsenic. J *Expo Anal Environ Epidemiol*. 2003;13(3):231-239.

(18) Lewis DR, Southwick JW, Scanlan LP, et al. The feasibility of epidemiologic studies of waterborne arsenic: a mortality study in Millard County, Utah. *J Envir Health*. 1998;60(9):14.

(19) Welch AH, Lico MS, Hughes JL. Arsenic in ground water of the western United States. *Ground Water*. 1988;26(3):333-347.

(20) Utah Department of Health, Panichello JD. Health Consultation: Arsenic Exposure in Culinary Drinking Water, Millard County, Utah. Agency for Toxic Substances and Disease Registry. 2009. (http://www.atsdr.cdc.gov/hac/pha/ArsenicExposureinMillardCountyUT/ArsenicExposureinUtahHC09-30-2009.pdf) (Accessed February 8, 2011).

(21) Lewis D, Southwick JW, Ouellet-Hellstrom R, et al. Drinking water arsenic in Utah: a cohort mortality study. *Environ Health Perspect*. 1999;107(5): 359-365.

(22) Centers for Disease Control and Prevention. Stillbirth. (http://www.cdc.gov/ncbddd/bd/stillbirths.htm) (Accessed February 14, 2011).

(23) Utah Department of Health. IBIS, Indicator-Based Information System. (http://ibis.health.utah.gov/home/Welcome.html) (Accessed March 23, 2008).

(24) California Environmental Protection Agency. Evidence on developmental and reproductive toxicity of inorganic arsenic. (http://ww.oehha.ca.gov/ Prop65/AS-HID.pdf) (Accessed October 15, 2008).

(25) Concha G, Vogler G, Lezcano D, et al. Exposure to inorganic arsenic metabolites during early human development. *Toxicol Sci*. 1998;44(2):185-190.

(26) Engel RR, Smith AH. Arsenic in drinking water and mortality from vascular disease: an ecologic analysis in 30 counties in the United States. *Arch Environ Health*. 1994;49(5):418-427.

(27) He W, Greenwell RJ, Brooks DM, et al., Arsenic exposure in pregnant mice disrupts placental vasculogenesis and causes spontaneous abortion. *Toxicol Sci*. 2007;14:175.

(28) Myatt, L, Cui X. Oxidative stress in the placenta. *Histochem Cell Biol*. 2004;122:369-382.

(29) Rahimian J, Varner MW. Disproportionate fetal growth. In: DeCherney AH, Nathan L, eds. *Current Obstetric & Gynecologic Diagnosis & Treatment, Ninth Edition*. New York, NY: McGraw-Hill; 2003:301-314.

(30) US Environmental Protection Agency. Public Drinking Water Systems: Facts and Figures. (http://www.epa.gov/ogwdw/pws/factoids.html) (Accessed October 12, 2008).

(31) US Census Bureau, American FactFinder. (http://factfinder.census.gov) (Accessed November 10, 2010).

(32) US Department of Agriculture, Economic Research Service. Rural-Urban Commuting Area Codes. (http://www.ers.usda.gov/Data/RuralUrban CommutingAreaCodes) (Accessed September 18, 2010).

(33) Canfield MA, Ramadhani TA, Langlois PH, et al. Residential mobility patterns and exposure misclassification in epidemiologic studies of birth defects. *J Expo Sci Environ Epidemiol*. 2006;16(6):538-543.

(34) Fell DB, Dodds L, King WD. Residential mobility during pregnancy. *Paediatr Perinat Epidemiol*. 2004;18(6):408-414.

(35) Khoury MJ, Stewart W, Weinstein A, et al. Residential mobility during pregnancy: implications for environmental teratogenesis. *J Clin Epidemiol*. 1988;41(1):15-20.

(36) Lupo PJ, Symanski E, Chan W, et al. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. *Paediatr Perinat Epidemiol*. 2010;24(2):200-208.

(37) Chen L, Bell EM, Caton AR, et al. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. *Environ Res*. 2010;110(2):162-168.

(38) Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2000. *Morbidity and Mortality Weekly Report*. 2002;51(29):642-645.

CHAPTER 5

CONCLUSION

The purpose of this research was to investigate whether exposure to low to moderate levels of arsenic in drinking water in community water systems (CWSs) in Utah in 1989-2006 are associated with elevated levels of small for gestational age (SGA) birth, pregnancy-related hypertension (PRH), and/or stillbirth. Results of the study are summarized below.

Small for Gestational Age

While studies have looked at the effect of arsenic on lower birth weight (1-3), no studies to date, to my knowledge, have looked at whether SGA at individual weeks 22-44 is associated with arsenic exposure. In this study there was a small, but statistically significant increase in the risk of SGA with increasing levels of arsenic in drinking water; compared with arsenic levels less than 2.5 µg/L, the adjusted odds ratio (aOR) for arsenic levels at 5.1 to 9.9 µg/L in drinking water was 1.04, 95% confidence interval (CI) 1.00, 1.07 for SGA; and at levels 10 µg/L and above the aOR was 1.07 (CI 1.03, 1.12). The sample size for the analysis, after excluding multiple births, infants with birth defects, stillbirths, nonresidents, maternal addresses outside of CWS boundaries, and those with missing data on gestational age, birth weight, and maternal address, was 631,375 births.

The SGA study also yielded a finding that the risk of SGA increased significantly with each 1,000 feet increase in elevation. Compared with births at elevations less than 3,000 ft, the aOR for SGA increased with every 1,000 ft gain in elevation, to an aOR of 1.90 (CI 1.64, 2.19) for women residing above 6,000 ft.

Pregnancy-Related Hypertension

There was no statistically significant association found between exposure to elevated levels of arsenic in drinking water and pregnancy-related hypertension. Compared with tap water arsenic concentrations less than 2.5 µg/L, the aOR for those exposed to 2.5–5 µg/L was 0.97 (CI 0.93, 1.00); for those exposed to 5–10 µg/L, aOR 0.98 (CI 0.94, 1.02); and for those exposed to levels at or above 10 µg/L, aOR 0.99 (CI 0.93, 1.05).

Two studies in Bulgaria found increased risk of pregnancy related hypertension in women exposed to arsenic and other metals (4, 5); however, the exposure pathways investigated were air and soil and not drinking water. Only one other study investigated whether hypertension during pregnancy is associated with arsenic exposure (6); in that study, however, the investigators only assessed blood pressure during pregnancy, and did not investigate whether preeclampsia or eclampsia were elevated with increased arsenic exposure.

After excluding nonresident births and maternal addresses that were outside of CWS boundaries or that had inadequate address information recorded on vital records, the final sample size was 675,830.

Stillbirth

No statistically significant association was found between exposure to elevated levels of arsenic in drinking water at the levels found in Utah community water systems and stillbirth. Compared with women whose tap water arsenic concentrations were less than 2.5 µg/L, the aOR for those exposed to 2.5–5 µg/L was 1.15 (CI 1.00, 1.31); for those exposed to 5–10 µg/L, aOR 0.77 (CI 0.65, 0.91); and for those exposed to levels at or above 10 µg/L, aOR 0.88 (CI 0.70, 1.10).

Several studies have investigated whether stillbirth is associated with high concentrations of arsenic in drinking water, with mixed findings (3-6). These studies, however, were in areas with very high arsenic levels in drinking water. Arsenic reference levels in these studies ranged from 50-200 µg/L, compared with a 2.5 µg/L reference level in the Utah study.

After excluding multiple births; birth defects; fetal deaths due to trauma, maternal death, infection, or breech delivery; nonresident births and stillbirths; maternal residence outside of a CWS; and inadequate address information, the final sample size was 639,924, including 639,465 live births and 2,459 stillbirths.

Summary

These studies help to clarify the risks posed by low to moderate levels of arsenic on adverse birth outcomes. The large sample sizes and the use of almost all births among Utah residents over a 17-year period that were served by CWSs minimizes selection bias and provides adequate power to detect even small increases in risk, should they exist. While small, yet statistically significant increases in the risk of SGA births were observed, no such effects were seen for stillbirth or pregnancy-related hypertension.

One of the limitations of using a large population-based dataset is the lack of individual information about water use behaviors, which leads to errors in the estimates of exposure. Such errors may bias effect measures toward the null. A large sample size is needed, however, to have sufficient statistical power to assess the effects of low levels of arsenic in drinking water, particularly since there are many known risk factors for these outcomes. Future studies are recommended that account for individual variability in water consumption and household treatment, but the required sample size may be prohibitively expensive.

The study findings described in detail in Chapters 2-5 apply to arsenic exposure levels in drinking water that are low to moderate. The effects of arsenic were assessed in four categories of exposure – less than 2.5 µg/L (reference group), 2.5-5 µg/L, 5.1-9.9 µg/L, and 10 µg/L or greater. Only 3.7% of the population were exposed to estimated arsenic levels of 10 µg/L or greater. The median annual arsenic level in this category was only 11.7 µg/L, and less than 0.02% of the population were exposed to arsenic levels greater than 40 µg/L. Several studies have found an association between high levels of arsenic in drinking water and stillbirth; additional studies are particularly recommended to investigate whether there is an

association between high levels of arsenic exposure in drinking water and increased rates of pregnancy-related hypertension and small for gestational age birth.

References

(1) Yang CY, Chang CC, Tsai SS, Chuang HY, Ho CK, Wu TN. Arsenic in drinking water and adverse pregnancy outcome in an arseniasis-endemic area in northeastern Taiwan. *Environ Res*. 2003;91(1):29-34.

(2) Hopenhayn C, Ferreccio C, Browning SR, et al. Arsenic exposure from drinking water and birth weight. *Epidemiology*. 2003;14(5):593-602.

(3) Huyck KL, Kile ML, Mahiuddin G, et al. Maternal arsenic exposure associated with low birth weight in Bangladesh. *J Occup Environ Med*. 2007;49(10):1097-1104.

(4) Tabacova S, Little RE, Balabaeva L, et al. Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. *Reprod Toxicol*. 1994;8(3):217-224.

(5) Tabacova S, Balabaeva L. Environmental pollutants in relation to complications of pregnancy. *Environ Health Perspect*. 1993;101(suppl):27-31.

(6) Kwok RK, Mendola P, Liu ZY. Changes in blood pressure during pregnancy associated with drinking water arsenic exposure in Inner Mongolia, China. *Ann Epidemiol*. 2004;14(8):621-624.

(7) Milton AH, Smith W, Rahman B, et al. Chronic arsenic exposure and adverse pregnancy outcomes in Bangladesh. *Epidemiology*. 2005;16(1):82-86.

(8) Cherry N, Shaikh K, McDonald C, Chowdhury Z. Stillbirth in rural Bangladesh: arsenic exposure and other etiological factors: a report from Gonoshasthaya Kendra. *Bull World Health Organ*. 2008;86(3):172-177.

(9) Rahman A, Vahter M, Ekstrom EC, et al. Association of arsenic exposure during pregnancy with fetal loss and infant death: a cohort study in Bangladesh. *Am J Epidemiol*. 2007;165(12):1389-1396.